Episodic medication adherence in adolescents and young people with perinatally infected HIV

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Abstract

Due to the success of antiretroviral (ART) medications, youth perinatally infected with HIV (PHIV+) are surviving into adolescence and young adulthood – the first generation to do so. Factors which influence non-adherence to ART in this group are of particular importance to the development of effective assessments and interventions. Within-participant research is important given the significant prevalence of inconsistent ART adherence reported in the literature. Previous studies have focused on between-participants differences and tended to ask participants to estimate their adherence over a period of time. No quantitative episodic (or event-level) investigations, related to specific incidences of adherence or non-adherence, have been conducted previously in this area.

The present study aimed to address these gaps in the literature by investigating within-participant variation in episodic antiretroviral adherence informed by the Information-Motivation-Behavioural Skills (IMB) Model. The study explored situational variation between adherent and non-adherent events in information, personal motivation, social motivation, and behavioural skills. A secondary aim was to investigate whether situational differences in affect, or behavioural context were associated with episodic adherence.

Twenty-nine PHIV+ young people recruited from the Adolescents and Adults Living with Perinatal HIV (AALPHI) cohort completed questionnaires measuring psychological and behavioural variables. Paired t-tests and McNemar's chi-square

tests were used to analyse associations between behavioural and psychological factors related to adherent and non-adherent events.

Weekend days, being away from home and a disrupted daily routine were associated with episodes of non-adherence. Lower reported behavioural skills and lower positive affect were associated with non-adherent episodes. There were no significant effects of negative affect, information, personal or social motivation. A conditional logistic regression model including behavioural skills and positive affect was significantly predictive of non-adherent episodes, although each predictor was not statistically significant independently.

These findings are discussed in relation to previous antiretroviral adherence studies. Clinical and theoretical implications are discussed.

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Introduction

Adolescents and young adults with perinatally-infected HIV (PHIV+) require antiretroviral treatment (ART) to manage the virus. This medication has a high adherence requirement to be optimally effective and non-adherence can be problematic.

This chapter reviews the evolution of PHIV+ and discusses the challenges faced by adolescents in growing up with this newly chronic condition, particularly in reference to ART adherence. Methods of measuring adherence and theoretical models used to explain adherence behaviour are discussed. An outline of the research questions concludes this chapter.

HIV: general overview

Disease

The Human Immunodeficiency Virus (HIV), a type of retrovirus, was identified as the causative agent of Acquired Immune Deficiency Syndrome (AIDS) in 1983 after the first cases of AIDS were recognised in the USA two years earlier (Sharp & Hahn, 2011). HIV targets multiple cells of the human immune system, interacting with macrophages and dendritic cells and transferring to CD4 T cells in regional lymph nodes where the virus then replicates rapidly (Adler, Edwards, Miller, Williams, 2012). Infection with HIV causes a number of associated conditions varying from symptoms of primary infection (such as rash, fever, malaise, night sweats, sore throat), to serious diseases associated with a suppressed immune system, including: tumours, hepatitis, liver, lung, gut, skin, eye and kidney disease, and significant

neurological manifestations (Adler, Edwards, Miller, Williams, 2012). Following a progressive loss of CD4 cells, patients develop AIDS-defining conditions which, when left untreated, are likely to result in death.

Transmission

The HIV infection is transmitted via four main routes:

1. sexual intercourse (anal, oral, vaginal)
2. contaminated needles (intravenous drug users, needlestick injuries)
3. tissue donation (blood transfusion, organ transplants)
4. mother-to-child (in utero, at birth, via breastfeeding).

The most common route of infection globally is unprotected sexual intercourse. Transmission via sexual intercourse, or contamination of needles or tissue products, can be grouped as means of 'behavioural' transmission. 'Perinatal' transmission is a term also used for mother-to-child, or vertical transmission.

Left untreated and at high concentrations in the blood (measured by viral load; VL), HIV can be easily transmitted, causing considerable public health threat in some countries where treatments are not widely available. With successful suppression of the virus such that viral load is "undetectable", or under 75 copies (virus particles) in one millilitre of blood, the risk of transmission of HIV is very low ("What is viral load", 2015).

Prevention of mother-to-child, or perinatal, transmission is a World Health Organisation priority and subject of a 'Strategic Vision' report to reduce rates of

perinatal HIV infection (WHO, 2010). The WHO advocates a four-tiered approach to this: preventing primary infection of HIV among women of childbearing age, preventing unwanted pregnancy in women of childbearing age, preventing transmission of HIV from a woman to her child and providing appropriate care, support and treatment to mothers and their children living with HIV. Across Europe, this strategy has been operationalized via offers of effective medications to all HIV+ mothers and babies born to HIV+ mothers, relating to the third and fourth parts of the WHO strategy. Breastfeeding is also not recommended (Bamford et al., 2015; British HIV Association (BHIVA), 2009).

Population: UK & Global

Since the identification of HIV in the 1980s, approximately 60million people have been infected, resulting in over 25million deaths from AIDS, becoming one of the most lethal pandemics in recent history (Merson, O'Malley, Serwadda, & Apisuk, 2008). Although there are reports of HIV in every country in the world, the highest prevalence rates are among young adults in Sub-Saharan Africa. Across this region, on average, 3 in every 100 people between 15-24 have HIV; this figure is even greater in Malawi, Zambia, Lesotho, Mozambique, Zimbabwe, Swaziland, Uganda and South Africa (WHO, 2010). The most recent data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates 35million adults and children are living with HIV globally (UNAIDS, 2014). Of these, 24.7 million are living in Sub-Saharan Africa (UNAIDS, 2014). An estimated 108,000 adults and children in the United Kingdom live with HIV (Public Health England Report, 2014).

Paediatric Population

The most recent prevalence estimates from UNAIDS report 3.4 million infected children under 15 years (UNAIDS, 2013) and 2 million adolescents between 10 and 19 years worldwide (World Health Organization, 2013). The population prevalence data seldom distinguish routes of transmission, a methodological flaw often repeated in the research literature, making it problematic for drawing conclusions about particular populations (discussed further below) (Mofenson & Cotton, 2013). It is reasonable to assume most, but not all, children with HIV acquired the infection perinatally (PHIV+). Global HIV incidence of older children and teenagers is likely to include some behavioural means of infections (BHIV+), i.e. unprotected sex and injected drug use (Sohn & Hazra, 2013).

UK Paediatric Population

Fifty-nine clinics across the UK report data on all HIV-infected children known to follow-up as part of the Collaborative HIV Paediatric Study (CHIPS). This has given researchers a comprehensive indication of how many PHIV+ young people are currently living in the UK. The most recent data, in March 2014, indicate a total of 1873 children receiving HIV care, from 2006 onwards. Of these, 108 children had died and 595 young people transitioned to adult clinics. Fifty-five percent of these young people were born outside the UK or Ireland. As of March 2014, a total of 1037 HIV-positive young people (median age 13) were alive and actively followed by paediatric clinics, of whom 96% were perinatally-infected. Seventy-nine percent are of Black African ethnicity. Half of the young people are seen at London clinics (Collaborative HIV Paediatric Study (CHIPS), 2014).

Treatment: Antiretroviral Therapy (ART)

The first antiretroviral treatment for HIV, a single nucleoside analogue reverse transcriptase inhibitor (NRTI) called azidothymidine (AZT), was not introduced until four years after the virus was discovered (Ruprecht, et al, 1986). Until this time, patients with HIV were treated by managing complications and opportunistic infections only.

In 1996, trial data of combination (cART) or highly active antiretroviral therapy (HAART) (hereafter referred to as antiretroviral therapy, ART) were presented at the 11th International Conference on AIDS (1996). These drugs were introduced to combat the virus at various stages of its lifecycle. ART became available in the USA and UK between 1997-8 and has significantly improved mortality and morbidity rates (Mellins & Malee, 2013; Judd, Doerholt, et al, 2007). The availability of medication varies according to country: access is growing but remains limited in resource-limited countries, including some Sub-Saharan African nations (UNAIDS, 2014).

Since the introduction of ART, there have been several pharmacological developments. To date, there are over 25 antiretroviral agents falling into six classes of treatment: NRTIs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and fusion or entry inhibitors (BHIVA, 2014). ART is available in the form of: dispersible tablets, tablets, granules, powders, capsules, and dispersible tablets for suspension. Combinations of these drugs are now available in

fixed dose pill combinations to help to reduce pill burden, which has an impact on adherence (BHIVA, 2009). The side effects of newer ARTs are fewer than older drug formulations, but long-term toxicity data are limited (Bamford et al., 2015).

Paediatric ART

Paediatric ART regimens were developed much later than adult formulations, with antiretroviral therapy not approved for children at all until the 1990s ("Guidelines and recommendations", 2015). Children born in the 1980s and early 1990s were either untreated or treated with suboptimal regimens (Chandawani, et al, 2012). There is paucity of child- and adolescent-specific ART trials. Instead, guidelines for prescribing in this population are drawn from cohort studies, extrapolating from adult data and expert opinion (Bamford, et al, 2015). The lack of specific data for children and adolescents increases the risk of ineffective ART regimens.

Perinatally Infected HIV+ Adolescents and Young Adults

Today's adolescents and young adults with perinatally infected HIV (PHIV+) are a unique group of young people: they are the first generation to have acquired the infection through vertical transmission and live into their teenage years and beyond. Children born with HIV infection before 1995 were expected to experience catastrophic consequences of their illness. Pre-1995 births carried twice the risk of the HIV-infected child developing AIDS-defining conditions or dying before age 5, compared to HIV+ children born after this time (Small et al., 2014). Data from 1996 report over 60% of children diagnosed with HIV and living in New York City, USA,

died before reaching adolescence (New York City Department of Health and Mental Hygiene, 2013).

The risks of disease progression are similar between adults and PHIV+ youth from the age of 5 and older (Bamford et al., 2015). However, there are key differences between these two populations, outlined below.

Developmental Issues

Adolescence is a time of psychosocial, biological and neurocognitive maturation (Suris, et al, 2004) during which young people experience significant growth and pubertal changes. Development of social identity, intimate relationships and occupational life skills occur during this time, as well as sexual experimentation and risk-taking behaviours (Taddeo, Egedy, & Frappier, 2008).

There may be a reciprocal and complex interaction between chronic illness (including PHIV+) and adolescent development. That is, the condition can impact on particular biological, psychological or social developmental processes, but psychosocial changes and adjustments can also impact on the illness: the timing of development in one area may affect the other(s) (Suris, Michaud, & Viner, 2004). In the case of PHIV+, the virus can affect bone mass density and bone mineral concentration (Pitukcheewanont, Safani, Church, & Gilsanz, 2005), even if the young person is taking ART (de Lima et al., 2013). PHIV+ young people are more likely than perinatally-exposed but not infected (PHIV-) controls to have abnormal body fat distribution related to cardiovascular disease risk as a result of both primary

infection with HIV and side effects of ART (Jacobson et al., 2011). The increased calorific requirement for growth during puberty may compound these issues (Suris et al., 2004; Suris & Parera, 2005)

Puberty may be impaired or delayed as a result of PHIV+, compared to age-matched PHIV- and HIV unexposed controls (de Martino, Tovo, Galli, Gabiano, & Chiarelli, 2001; Williams et al., 2013). ART has brought forward pubertal onset in adolescents depending on birth cohort: youth born after 1997 may have better outcomes due to the availability of optimal treatments since birth, although the mechanisms of and interactions between PHIV+ exposure, ART medications and the processes of puberty remain poorly understood (Adler, et al, 2012; Williams et al., 2013). For those PHIV+ young people who may experience disturbance in normative puberty, this may have a subsequent impact on delayed sexual maturity, formation of intimate relationships and self-esteem, which may all, in turn, increase the risk of mental health problems (discussed further in 'Psychosocial issues' below) (Mellins & Malee, 2013).

During adolescence, executive control functions are refined, leading to a more self-directed and self-regulating mind (Laughton, Cornell, Boivin, & Van Rie, 2013). Although the adolescent brain does not grow larger, there is reorganisation and maturation of the neural pathways, which is evident in changing cognitive performance and observable behaviour, such as risk-taking and impulsive action (Steinberg, 2005). Key components of these changes are developments in: working

memory, processing speed, voluntary response inhibition, cognitive flexibility, rule-guided behaviour, abstract thinking and response planning (Luna, 2009). All of these processes are central to health behaviours and crucial as adolescents take over control of their own healthcare from their caregivers during transition to adulthood.

There is a paucity of research in the area of cognitive capacities of PHIV+ young people during adolescence, however, with a larger focus on younger (age 6-12) or older (age 7-16) children to the neglect of older teenagers and young adults (Puthanakit et al., 2013; Smith & Wilkins, 2014; Smith et al., 2008). There is considerable heterogeneity in testing and measurement of the neurocognitive correlates of PHIV+ infection in adolescents, particularly in resource-limited countries (Laughton et al., 2013).

The effect of HIV on cognitive functioning may not be reversed despite initiation of ART. In one cohort of PHIV+ Thai children, there was no improvement in cognitive function following commencement of ART, even when virological suppression and immunological recovery was achieved (Puthanakit, Aurpibul, Yoksan, Sirisanthana, & Sirisanthana, 2010; Puthanakit, Aurpibul, Louthrenoo, et al., 2010). There may also be neuropsychological sequelae associated with ART toxicity (or adverse drug reactions) in children and young people, including bad dreams, mood swings, drowsiness, dizziness, impaired learning and depression (Bamford et al., 2015; Welch et al., 2009). Studies in the USA and Europe have demonstrated significantly

poorer overall cognitive development for adolescents on ART compared to national norms (Laughton et al., 2013).

PHIV+ may impact on the normative development of independence during adolescence, characterised by poor mastery of activities of daily living. A single investigation into differences between age-matched PHIV+ and PHIV- young people found lower mastery of daily living and self-care skills as measured be self- and caregiver report (Pearlstein et al., 2014). However, these effects were not significant when controlling for age, gender, verbal ability and psychiatric functioning and have not been replicated, so must be interpreted with caution.

Long-term exposure to the HIV virus is likely to result in underlying inflammation and suboptimal immune system function, even with effective treatment (Bamford et al., 2015; Siberry et al., 2011). Therefore, PHIV+ adolescents may have experienced an increased number of common infections or illnesses throughout childhood and may have a number of experiences in common with other young people with chronic illnesses such as continuing contact with medical professionals, pain and missed school (Persson et al., 2014). There may also be unique implications of growing up with PHIV+ that set apart these young people from other adolescents with chronic illness.

Psychosocial Issues

PHIV+ young people are put at risk for poor psychological and behavioural outcomes globally by financial hardship, poor health care and limited access to education

(UNAIDS, 2014). Furthermore, they are more likely to have experienced the death or serious illness of one or both parents (Kang et al., 2008; Kang et al., 2008). PHIV+ youth may have increased genetic vulnerability for mental health and substance abuse problems, indicated by high rates of both in HIV+ parents. Cohort studies across cultures consistently suggest high rates of behavioural and emotional health problems in PHIV+ youth (Bomba et al., 2010; Mellins et al., 2012; Mellins et al., 2011; Menon et al., 2007; Puthanakit et al., 2013).

PHIV+ young people are set apart from HIV+ adults and BHIV+ youth in that they are born into families with prior experience of HIV (Cluver, Gardner, & Operario, 2008). Families may have experienced prolonged discrimination and stigma (Nyblade, Stangl, Weiss, & Ashburn, 2009).

ART Adherence

Adherence is defined by the World Health Organisation as, "the extent to which a person's *behaviour* – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO, 2003). Exact optimal adherence figures vary according to specific requirements of a particular regimen. ART adherence of greater than 90-95% is generally considered necessary to maximise effectiveness and prevent resistance (BHIVA, 2014). Adherence to ART is a good predictor of clinical outcome and has led to reductions in morbidity and mortality from AIDS globally. However, in young people age 10-19, mortality rates are increasing, in part due to lack of support for ART adherence, as well as poor prioritisation of adolescents in public health planning

and a lack of acceptable healthcare services for this age group, according to the World Health Organisation (WHO, 2013).

Suboptimal Adherence

The speed at which the HIV virus replicates necessitates near-perfect adherence to antiretroviral medication at all times to prevent progression of the disease and destruction of the immune system (Adefolalu & Nkosi, 2013). The likelihood of developing antiretroviral resistance increases with suboptimal medication adherence. This has implications not only for the individual in narrowing the available treatment options, but also for transmission risk to others. Medication-resistant strains of HIV can develop and, without adequate precautions, be transmitted easily and unknowingly, causing an increasingly virulent epidemic (Murphy, Marelich, Rappaport, Hoffman, & Farthing, 2007). Adherence rates for the PHIV+ population are presented later in this chapter.

Adherence Guidelines

With changing ART formulations, there have been numerous iterations of ART prescribing guidelines for adults, young people and children. The number of CD4 cells in a blood sample is often used to determine if and when ART should be initiated. A normal range in adolescents and adults is between of 500-1200 cells/µl and indicates good function of the immune system; a low or falling CD4 count may indicate damage to the immune system and progression of HIV ("What is a CD4 cell", 2014). At present, the European recommendation is to commence ART in children over age 5 and adults when CD4 approaches <350cells/ µl; the WHO and US

guidelines recommend starting at <500cells/ µl (Bamford et al., 2015; WHO, 2014) Initiation is also recommended in children where there is delay in growth or onset of puberty, neurocognitive delay, at the request of the child or family, when adolescents become sexually active and during pregnancy (Bamford et al., 2015). Prior to commencing ART in both adults and children, a thorough assessment of readiness and preparedness to adhere to the regimen is recommended in most national guidelines (Bamford, et al, 2015; BHIVA, 2014; Children's HIV Association, 2013). If barriers to adherence are identified, prescribers are encouraged to delay initiation of ART and endeavour to address such barriers. The British HIV Association recommend a thorough assessment of individual barriers and formulation of strategies to manage, although there are no clear guidelines for how to assess barriers or what specific strategies may be most useful.

PHIV+ ART Adherence

Following the pivotal development in HIV treatment, introduction of ART, the epidemic has "changed face" from a terminal prognosis to a chronic, life-long condition in resource rich countries with effective treatment (Mofenson & Cotton, 2013).

The purpose of treatment for HIV infection has evolved from short-term management of co-morbid illnesses and limiting mortality to promotion of quality of life and minimising symptoms to a near-normal life expectancy (Nakagawa et al., 2012). Although risk of death of PHIV+ children has reduced, the virus remains life threatening without adequate treatment management. As the first generation to

grow up with ART, predicted life expectancy and rates of mortality in perinatally infected young adults are unknown. A recent mortality audit of 248 PHIV+ young people who have transitioned to fourteen adult clinics in the UK found eleven deaths, with nine out of these associated with poor adherence to medication and concomitant advanced disease (Fish, Judd, Jungmann, O'Leary, & Foster, 2014). This highlights the great importance of investigating barriers to adherence in the PHIV+ population so that these young people can be supported to maintain optimal adherence to their ART regimens. Indeed, PENTA recommend adherence is explicitly discussed between patient and professional at every clinic visit (Bamford, et al, 2015).

Rates Of ART Adherence

A recent systematic review and meta-analysis was conducted of 51 studies reporting adherence for 10725 patients between 12-24 years old. This study found that only 62.3% were over 85% adherent to ART (Kim, Gerver, Fidler, & Ward, 2014). Measures of adherence included self-report in 13 studies or viral suppression (measured by undetectable viral load) in 36 studies, however there was little effect on the adherence estimates of different means of measurement. There were some differences between geographical regions with adherence in Africa and Asia higher than Europe, South America and North America. The authors suggest differences in the epidemic of HIV (generalised across the nation versus focused in particular sub-populations) as one possible explanation for this finding: HIV-infected adolescents in more developed countries may belong to more vulnerable, at-risk, marginalised groups with poorer access to adequate services in spite of greater national

resources. Kim and colleagues compare their findings of adolescent adherence to adult data. One cohort study across 17 European countries and a Brazilian study with almost 2000 participants demonstrated adult adherence was significantly greater than adolescent adherence in Europe and South America. These results reiterate the importance of adherence research in an adolescent group.

One problem with the findings in this review is the threshold for "adherence", set at 85% or over in a given time period, without a clear rationale. Optimal adherence is generally considered to be >90-95% to achieve effective virological suppression. The clinical implications for taking medication 85% of the time versus 95% could be argued to be significant. This highlights a methodological issue when measuring medication adherence: there is not a consistent or standardised means to classify good adherence or non-adherence. Measurement issues are discussed in greater detail below.

Adolescents are consistently found to be significantly less adherent to ART than younger children (Arrivillaga, Martucci, Hoyos, & Arango, 2013; Malee et al., 2011; Merzel, VanDevanter, & Irvine, 2008) and adults (Nachega, Hislop, & Nguyen…, 2009). In an observational cohort study of nearly 8000 adolescents (age 11-19) and adults (age >19) in Southern Africa, the young patients were less likely to be 100% adherent or achieve immunological recovery as measured by CD4+ count (Barclay et al., 2007). Given the numerous developments that occur during adolescence, it may follow that a young person's adherence at this time is not necessarily stable. Rather it may be a dynamic function of developing cognitive and psychosocial capacities

(Hanghøj & Boisen, 2014; Simoni et al., 2007). However, PHIV+ adolescents may have lower rates of virological suppression and higher rates of ART resistance than HIV+ adults (Tassiopoulos et al. 2013), therefore understanding barriers to and promotion of adherence to first-line regimens is key to managing health outcomes in this population.

Of the UK PHIV+ population, according to the CHIPS project, in 2014: 40% were taking their first ART regimen, 37% were on a subsequent ART regimen, 7% were on mono- or dual-ART treatment, 11% were treatment naïve and 5% were not taking any antiretroviral drugs having taken them at some point previously (CHIPS, 2014). A change from first to subsequent regimen, or mono- or dual- therapy may implicate problems with resistance to a first-line treatment or ineffectiveness of a previous medication. It is not possible to ascertain for what reason the medication was changed from these data. However, it is possible that adherence problems could be linked with both medication resistance and ineffectiveness, which would both necessitate a change to an alternative regimen.

Measurement of adherence

A key difficulty in medication adherence research is a lack of standardised methods of measurement. As a result, many approaches are used, including: self-report, pill-count, biological markers (such as viral load), electronic monitoring, pharmacy-based records, provider estimation and therapeutic drug monitoring (Kim et al., 2014). The most common of these are discussed below.

Pill-count

Recording the number of pills prescribed at the start of the month minus the number remaining at the end is known as the pill-count method of adherence measurement (e.g. Murphy, Marelich, Rappaport, Hoffman, & Farthing, 2007). It is a robust method of adherence measurement that is significantly correlated with viral load across studies (Farley et al., 2008).

Pill count data is not as easy to collect as self-report as participants may neglect to bring in their medicine bottles to clinic or research appointments, which may lead to incomplete or missing information and an inaccurate overall adherence value. Furthermore, in paediatric populations in particular, some ART is prescribed in liquid form, which is much more challenging to measure accurately by a 'counting' method.

Biological markers

Another objective method of measuring non-adherence is by taking blood serum assays to measure CD4 count and HIV RNA viral load (Sherr et al., 2010). A lower CD4 count and a higher viral load are biological markers of non-adherence or resistance to ART. It may be impractical and costly for researchers to use blood tests to measure adherence, especially as one cannot be certain of the exact time frame of the non-adherence (particularly without a baseline blood result to compare to).

Real-time monitoring and prospective methods

There is a general reliance on global (over a specified period of time) and retrospective reports of adherence in the literature. Continuous, real-time monitoring is possible through the use of electronic, cellular or wireless internet

enabled devices, examples of which are the Medication Events Monitoring System (Barclay et al., 2007; Hardy et al., 2011) and Wisepill (Haberer et al., 2010). Each of these systems monitors when a medicines bottle or dosing box is opened and transmits a signal to record as such.

Advocates of these systems of measurement argue that they enable suboptimal adherence to be detected quickly and before any adverse effects of resistance or increased viral load progress (Haberer et al., 2010). However, the systems are costly, require training to use, may overestimate non-adherence and are, overall, not routinely practical (Usitalo et al., 2014).

Self-report

Adherence measurement by self-report is common, in spite of generally accepted flaws, because it is an inexpensive method with is feasible across settings (Chesney et al., 2000). There is a tendency for data collected in this way to overestimate adherence, possibly due to social desirability and ceiling effects (Usitalo et al., 2014).

In paediatric research, it is necessary to select between actual self-report and caregiver report. However, it has been found that adolescents are willing to openly disclose non-adherence through self-report (Hanghøj & Boisen, 2014; Staples & Bravender, 2002). When these data are checked against more objective measures of plasma HIV concentrations or detectable viraemia, there is a significant correlation, providing evidence of validity for self-reported adherence/non-adherence (Kahana, Rohan, Allison, Frazier, & Drotar, 2013)

One of the inherent biases in self-report is an individual's ability to recall past events. Conway's (1996) model of autobiographical memory asserts that such memories are organised hierarchically: remembering specific episodes elicits the most detail. Nevertheless, all remembering can be unreliable and must be scaffolded, or supported with temporal or thematic cues to promote an accurate account (Belli, 1998). These cues enhance the quality of retrospective report by triggering a similar perceptual context and a sense of 're-living' the event. Therefore, more details about the event can be recalled (Conway, 1996; Brewer, 1996). These principles are relied upon in the Cognitive Interview, used by the criminal justice system to enhance the reliability of witness memory (Schwarz, 2007).

Research designs using the Day Reconstruction Method (DRM) aim to promote accurate remembering of episodic memories. DRM involves remembering the context of a daily event to reconstruct the subjective experience and minimise recall bias (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004). In the original description of this method, participants were asked to reconstruct the previous day. This is particularly important in the recall of affective states, due to the confounding influence of post-hoc decontextualized beliefs about emotion (Robinson & Clore, 2002). By invoking the contextual details of an event, more specific memories are elicited thereby reducing recall bias and remembering error (Kahneman et al., 2004).

Other methods designed to minimise recall bias include prospective experience

sampling methods such as Ecological Momentary Assessment (EMA). EMA is a repeated sampling method of data collection measuring participants' subjective experience and behaviours in real time in 'natural' environments (Moskowitz & Young, 2006). One strategy of EMA is event-based monitoring, where assessments are triggered by a predetermined event. Such reports, however, can be subject to error due to poor compliance, or participants deviating from the research protocol and assessment schedule (Shiffman, Stone, & Hufford, 2008), and attrition rates for prospective research are high.

The DRM and EMA have been compared in a study of fatigue and momentary changes in mood over a fixed period, with no significant differences in the results from each design. Although EMA may be superior in measuring momentary changes over time, for a fixed study period DRM appears to be comparable in minimising bias in retrospective report (Kim, Kikuchi, & Yamamoto, 2013).

Factors associated with adherence

There are significant consequences to not taking ART medication as prescribed. However, insufficient adherence is problematic across a number of chronic illnesses and across the lifespan, presenting a particular challenge during adolescence (Simoni et al., 2007). There is a considerable interest amongst health services to investigate adherence difficulties between individuals and barriers to optimal adherence have been studied across conditions, in adults and teenagers.

There are numerous ways to categorise types of adherence barriers. In a review across asthma, cancer, depression, diabetes, epilepsy, HIV, hypertension, smoking cessation and tuberculosis, the World Health Organisation describe five factors important to treatment adherence: social and economic factors, health care team and system related factors, condition related factors, therapy related factors and patient related factors (WHO, 2013). The following section presents selected research into the correlates of ART adherence between individuals according to the WHO categories of treatment-related and patient-related factors. A review of the higher order factors of social, economic, health system and disease influence is beyond the scope of this thesis. Treatment- and patient-related factors are selected as most proximal determinants of adherence related to individuals.

Treatment-related factors

Regimen

ART regimens carry a significantly greater burden than the treatment for many other chronic medical conditions (Buchanan et al., 2012). A 2000 study reported that ART regimens in adults consisted of an average of fourteen tablets daily (Murphy et al., 2003). Pill burden has reduced in recent years with single-dose preparations becoming available in 2006 (Nachega et al., 2014). The latest World Health Organisation guidelines advocate single-dose regimens, while some drugs still require up to five pills per dose to be taken (WHO, 2010). A 2012 study in adolescents cited a mean number of prescribed tablets at six and a half per day (Chandwani et al., 2012).

Increased treatment burden is likely to be associated with poorer adherence. In a recent meta-analysis of randomised control trials in adults, lower pill burden was associated with increased ART adherence; a once-daily regimen was related to better adherence compared with twice-daily regimens (Nachega et al., 2014). Perceived difficulty of medication routine is associated with non-adherence in adults and adolescents (Williams et al., 2006), with both perinatally and behaviourally acquired HIV (Chandwani et al., 2012). Complex regimens have been associated with forgetting to take medication (an often-cited barrier to adherence discussed below) (Murphy et al., 2003).

Side effects

Unwanted adverse effects are a considerable barrier to adherence amongst the PHIV+ population (e.g. Macdonell, Naar-King, Murphy, Parsons, & Huszti, 2011). These young people express difficulties in tolerating some ART medication, possibly due to being on less palatable preparations as a result of drug resistance. However, the distinction between exact drug regimens is seldom reported in the literature so this suggestion is a tentative one.

Patient related factors

Caregiver/family factors

As adolescents strive for more autonomy and independence within their family, help offered from relatives can be interpreted either as a stressor or support. Parents and carers must balance the increased need for personal responsibility whilst not over-burdening a young person with obligations for which they are ill-equipped, that

is, being solely responsibly for their ART medication (Neinstein, 2008). In a cross sectional study of families including children (mean age 7, range 3-13) and their caregivers, responses were compared across those who reported missed doses (nonadherent) or no missed doses (adherent) over the past month. Non-adherence was significantly associated with older child age, higher caregiver stress, worse parent-child communication, and poor caregiver quality of life. When age was controlled for, worse parent-child communication and higher caregiver stress were strongly associated with non-adherence (Mellins, Brackis-Cott, Dolezal, & Abrams, 2004). This study was carried out in younger children, however did include some teenagers. That family factors remained significant when controlling for age may indicate continued influence on adherence as young people enter adolescence.

Research indicates involvement of caregivers varies greatly during adolescence and may be based on the age and health-status of the adolescent patient (Denison et al., 2015). The extent to which young people are able to take ownership of their healthcare may not be solely related to their personal motivation, skills and abilities, but may also be influenced by willingness of caregivers to allow the young people to assume responsibility. Naar-King and colleagues found a quarter of PHIV+ young people aged between eight and 18 reported being fully responsible for taking their medication (2009). Degree of responsibility increased with age, but age was unrelated to adherence; successful transition of responsibility was associated with increased ART adherence. There is some indication in the literature that familial support can be important in successfully transitioning from paediatric to adult health

services in Australia (Newman, Persson, Miller, & Cama, 2014), Zambia (Denison et al, 2015) and the UK (Foster et al., 2009).

Transitioning

Children who acquired HIV at birth have relied on adult caregivers to look after their health for a significant period of their lives, unlike individuals infected in adulthood who commence treatment for which they are solely responsible. PHIV+ young people must go through a period of transition as they begin to take increasing ownership of their own healthcare (Buchanan et al., 2012; Koenig, Nesheim, & Abramowitz, 2011).

In resource rich countries, children with PHIV+ have experiences of paediatric services, characterised by multi-disciplinary, family-centred working with access to numerous support services. By contrast, adult clinics assume the individual's responsibility for their own care (Mofenson & Cotton, 2013). In the UK, CHIVA recommend transition services where local healthcare provision allow, whereby adult and paediatric services offer co-ordinated multidisciplinary clinics to ensure the handover of care happens without young adult patients being lost to follow up (Foster et al., 2009; CHIVA, 2013). Weiner and colleagues conducted semi-structured interviews with 59 HIV+ participants who were in the process of, or had transitioned, from paediatric to adult care in the USA (Wiener, Kohrt, Battles, & Pao, 2011). Almost half reported difficulties with adherence during the changeover period, which was evident in lower CD4+ counts in those who had transitioned to adult care on measures of pre- and post-transition (p=.08).

Stigma & disclosure

Stigma and misconceptions about HIV are prevalent in much of society, causing HIV+ individuals to feel a need to conceal their diagnosis and maintain a level of secrecy (Simoni et al., 2007).

In a US focus group of 25 HIV+ young people, half of the participants reported deliberately missing a dose of ART due to fear of inadvertently disclosing their status to a friend or family member (Rao, Kekwaletswe, Hosek, & Martinez…, 2007). This focus group contained only one PHIV+ young person, but it is likely that the impact of stigma may be just as great between PHIV+ and BHIV+ young people. In support of this, Abramowitz and colleagues found BHIV+ adolescents (age 13-21) had disclosed their HIV status to significantly more friends or people outside the family than their PHIV+ peers (Abramowitz et al., 2009).

Researchers in Uganda suggest HIV+ children become aware of HIV-related stigma from a young age and respond to adult instructions to maintain secrecy (Kawuma, Bernays, Siu, Rhodes, & Seeley, 2014). In interviews with 26 older children (age 11-13), these authors found, contrary to their hypothesis that forgetting would be a main reason for non-adherence, not wanting to be seen by others was key to not taking their ART medication.

These findings were replicated in an adolescent sample in Zambia. Interviews with young people (age between 15 and 18 years) and their adult care-givers in Zambia elicited fear of stigma and disclosure as key reasons for not adhering to ART

medication (Denison et al., 2015). Management of HIV was reported to be restricted to the home environment and young people reported concerns regarding anticipated stigma, or expectation of future discrimination (Earnshaw & Chaudoir, 2009) if they took medication outside of their home. Peer support groups with links to their clinic were the only exception, where participants reported feeling encouraged and accepted such that they were comfortable in taking their medication in the group outside their home.

Neurocognitive factors

Deficits in neurocognitive development may equate to deficits in the general cognitive processes involved in taking medication. Adherence to ART requires personal organisation and adequate cognitive skill. Non-adherence may be due to poor abstract thinking ability, manifesting in poor planning and preparatory techniques, or a poor perception of risk or future consequences (Malee et al., 2009). Executive functions such as initiation, processing speed, voluntary inhibition, flexibility of thinking and following rules can be impaired in PHIV+ and therefore impair an individual's ability to adhere to a medical regimen (Laughton, Cornell, Boivin, & Van Rie, 2013). In a New Zealand cohort of typically developing adolescents, performance on neuropsychological and executive function tests was significant predictors of risk taking (Pharo, Sim, Graham, Gross, & Hayne, 2011). Non-adherence has frequently been classified as a risk-taking behaviour, therefore there may be some influence of executive function impairment on ART adherence (Laughton, Cornell, Boivin & Van Rie, 2013)

PHIV can affect frontal brain regions impacting on emotional and behavioural regulation (Smith & Wilkins, 2014), which may also account for comparatively more psychiatric symptoms in the PHIV+ population (Chernoff et al., 2009; Gadow et al., 2010, 2012).

Mental Health

PHIV+ individuals are more likely to be diagnosed with mental health disorders, such as depression, than their HIV- peers (Mellins & Malee, 2013). This can interfere with ART adherence motivation and the ability to enact motivation. The psychosocial correlates of increased mental health disorder are discussed above (in 'Perinatally Infected HIV+ Adolescents and Young Adults'.

In support of this relationship, in PHIV+ women during pregnancy, a significant difference in ART adherence and viral load at time of delivery has been found between those with and without a history of depression (Sheth et al., 2015).

The LEGACY (Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth) study in the USA is a prospective, multi-site cohort study of HIV+ youth comprising 197 PHIV+ young people age 13 and older. Over half the sample had documented psychiatric diagnoses, current or historic, and 72% had ART adherence problems as documented in their medical notes. Psychiatric morbidity was associated with risky behaviour (including treatment non-adherence, substance misuse and preadult sexual activity) in multivariate analysis (Kapetanovic et al., 2011). However, other research between "good adherers" and "poor adherers" has

suggested no differences in mental health disorders between groups (Rudy, Murphy, Harris, Muenz, & Ellen, 2010).

Self-efficacy

Self-efficacy in relation to medication, refers to one's perceived abilities to be able to adhere to a medication regimen as prescribed. It is consistently related to adherence to treatment or therapy regimes in research with adults and adolescents across conditions, including renal disease (Vasylyeva, Singh, Sheehan, Chennasamudram, & Hernandez, 2013) and diabetes (Griva, Myers, & Newman, 2000).

In PHIV+, mean ratings on a scale of self-efficacy were significantly higher in good versus poor adherers in a large sample (n=368) of PHIV+ youth (age 12-24) in USA (Rudy et al., 2010). In a study of ninety-two Thai PHIV+ youth recruited from clinic settings, higher ratings of self-efficacy were associated with higher levels of ART adherence, measured by self-report over the past 30 days (Kang, Delzell, Chhabra, & Oberdorfer, 2014). This is in keeping with previous findings in adolescent populations in the USA, where correlations were found between self-efficacy and adherence in a sample of both BHIV+ and PHIV+ aged between 16-24. When controlling for psychological distress, self-efficacy independently predicted adherence in this group (Naar-King et al., 2006).

Self-efficacy has frequently been measured in cross-sectional studies in relation to medication adherence. Momentary variation in self-efficacy has also been studied in

adolescents attempting to quit smoking (Van Zundert, Engels, & Kuntsche, 2011). Researchers found situational variation in young people's confidence to enact smoking cessation behaviours. Although self-efficacy was measured with a single question, this was repeatedly asked across a number of days. This approach might suggest that daily, or episodic (relating to particular events), as well as global (over a longer period of time) self-efficacy could be influential in adherence behaviours.

Only one study has explicitly investigated daily variation in medication-related self-efficacy. In a study of adult beta Thalassaemia Major patients, the researchers found significant differences in self-efficacy *within-participants* between an adherent episode and a non-adherent episode (Vosper, Evangeli, Porter, & Shah, 2013).

Routine

The extent to which structure and routine are built into an individual's lifestyle are important factors in ART adherence. A young person being away from their home or usual surroundings is a commonly cited barrier to adherence, as is difficulty in scheduling doses so that they become incorporated into one's usual routine (Murphy et al., 2003; Rudy, Murphy, Harris, Muenz, & Ellen, 2009; Buchanan et al., 2012).

A qualitative investigation of ART adherence in suboptimally adherent HIV+ adults in California, USA, investigated the level of structure of daily schedules and adherence (Saberi, Comfort, & Johnson, 2012). Participant interview data was grouped into: 'not organised', characterised by no recurring daily activity at all; 'somewhat

organised', characterised by the recurrence of one or more regular activities; or 'highly organised', where medication was linked to a regular structured activity. Participants in the 'not organised' group were uniformly non-adherent, at a rate of 0% as measured by self-report over the previous 30 days. Participants in the 'somewhat organised' or 'highly organised' groups reported greater adherence of >70% and 93-100% respectively, even if their living situation was unstable. That is, the presence of at least one structured activity appeared to be associated with increased ART adherence. However, the conclusions from this study are tentative due to a small sample size (n=14) and a lack of inferential statistical analysis.

A longitudinal study measuring types of barrier to ART adherence across four separate clinic visits in HIV+ adults revealed at least one problem with daily structure or routine in 66% of 503 appointments (Genberg, Lee, Rogers, & Wilson, 2014). This was the most frequently cited barrier to ART adherence and was associated with reduced levels of adherence over time, as measured by an electronic monitoring system. Genberg and colleagues report these results as supportive of similar findings in other research in HIV+ populations in developing and developed countries (MacDonell et al., 2013; Mills et al., 2006; Murphy et al., 2003).

Following structured interviews with BHIV+ young people and medical record review, Murphy and colleagues compiled a list of 19 potential barriers to adherence (Murphy et al., 2003). A further 114 BHIV+ adolescents (age 12-19) were asked to rate, depending on how often they experienced each barrier; scores ranged from

'never' to 'often' on a four-point scale. Combining 'sometimes' and 'often' responses, two of the three most endorsed reasons for non-adherence in this group were related to daily activity or routine: did not have medication with them (42%) and change in daily routine (33%); the third reason was simply forgetting (46%). It is possible that similar barriers may apply to PHIV+ adolescents. In a survey of PHIV+ and BHIV+ young people MacDonell and colleagues adapted the 19 potential barriers from Murphy and colleagues' investigation, to investigate possible differences between groups (MacDonell et al., 2013). Participants were required to respond with 'yes' or 'no' depending on whether each factor had interfered with their adherence over the past seven days. The authors found no significant difference between groups' endorsement of "got in the way of my daily schedule" as a barrier to adherence. Therefore, difficulties in daily routine may contribute to nonadherence in PHIV+ youth.

These findings suggest routine is a key determinant of ART adherence. However, routine may vary over time, which may differentially influence ART adherence in particular contexts. Each of these investigations neglects potential contextual influence, which could be measured in relation to ART adherence in PHIV+ young people.

Forgetting

Not all non-adherence is intentional or conscious, rather forgetting is an often-cited, significant explanation for failing to take medication (e.g. Buchanan et al., 2012; Macdonell, Naar-King, Murphy, Parsons, & Huszti, 2011; MacDonell et al., 2013). In

a sample of PHIV+ 120 children and young adults (age >8-19) and their caregivers, participants were supplied with possible reasons for missing ART doses and asked to rate how often they/their child missed their medication due to each factor (on a scale of never to always). Forgetting was the most common reported barrier amongst both PHIV+ youth and their caregivers (Buchanan et al., 2012).

Somatic symptoms

In a Nigerian study of children (age 3 to 18), the most common reasons for non-adherence, as reported by caregivers and young patients, were due to being asleep or because of vomiting. Although these children were of a young age, feeling physically well or unwell has been linked with adherence in other chronic conditions in adults, children and adolescents (Hanghøj & Boisen, 2014). In HIV+ participants age 16-24, experiencing physical symptoms such as rash or headache, or feeling sick or vomiting were rated as most likely to cause non-adherence amongst those young people who were prescribed ART (Macdonell et al., 2011). Between groups of optimal and suboptimal adherers, the experience of adverse physical symptoms was rated most highly as a barrier to adherence in adolescents with less than 90% adherence in the previous month. (This study is discussed further in regard to substance use, below, and within-participant differences in adherence, in a later section (p 43).)

Substance use

Alcohol and substance misuse is prevalent amongst teenagers and young adults. Age at first use of marijuana was significantly predictive of self-reported non-adherence in 42 adolescents age 16-25 with HIV (Hosek, Harper, & Domanico,

2005). It was not clear in this study by which route the participants were infected. HIV+ adolescents (n=186) were asked to predict possible factors that may tempt them not to take ART. Being drunk or high was rated as the reason fourth most likely to be a barrier to adherence (behind physical symptoms, vomiting and forgetting) (Macdonell et al., 2011). In this sample, however, not all participants were prescribed ART medications. Of those prescribed ART, there were no differences on situational temptation not to adhere due to being under the influence of alcohol or street drugs between optimal and suboptimal adherers. Furthermore, the HIV+ young people in this sample were both behaviourally- and perinatally-infected. Therefore, it is unclear to what extent substance use may influence adherence in an adolescent PHIV+ sample.

Critique of existing literature

The factors presented here frequently occur in the literature as barriers associated with adherence, but there are a number of methodological factors that prevent conclusive inferences about determinants of ART adherence in young people with PHIV+ from being drawn. Firstly, the samples of young people are often not clearly described in terms of route of transmission of the HIV infection. There are particular characteristics of perinatal HIV infection that set it apart from other long-term diseases or behavioural HIV infection, such as a history of suboptimal or ineffective ART regimen and more compromised health from greater exposure to HIV infection prior to the introduction of ART. Although comparisons can be made with adolescents growing up with other conditions, or with adults living with HIV, the combination of being an adolescent growing up with HIV must be considered when

studying adherence in this population. Secondly, some important constructs are not measured in the majority of the studies described above, such as normative beliefs about and attitudes towards ART, outcome expectancies, and affect. Thirdly, how barriers to adherence were assessed or how adherence was measured is not always stated; scales of established reliability or validity are rarely used in the above studies. Furthermore, in all of the studies described thus far, adherence is assessed over a period of time using averages and frequencies as a measure of *global* adherence, rather than focusing on specific adherent or non-adherent events as a measure of *episodic* adherence. Assessing adherence over a time period may be less reliable than asking participants about a specific episode. Much of the research into barriers or facilitators of adherence reports on self-reported reasons for generally adhering or not adhering to their medication. Cited reasons may not be reliable due to a lack of insight into what causes non-adherence. In addition, the ways in which these constructs are measured in relation to adherence or non-adherence is mostly cross-sectional and assesses adherence differences between individuals. There is little understanding of how factors relating to adherence may vary within an individual. (The limited literature on within-participants medication adherence is discussed in the following section.) Finally, there is a paucity of adherence research informed by health-behaviour theory. This is discussed further in a later section of this chapter, 'Health Behaviour Theory'.

Within-Participants Research

The majority of existing research in HIV focuses on between-subjects correlates of ART adherence whereby comparisons are made between generally 'good adherers' and 'poor adherers' reporting their adherence over a period of time (Nichols et al., 2012; Rudy et al., 2009). Much less attention has been paid to within-participant variation in adherence. Adherence is not a stable trait; research suggests 40-50% of patients across conditions are 'inconsistently adherent', intentionally or unintentionally skipping doses or taking breaks from medication for longer periods (Bosworth et al., 2012). Therefore within-participant designs allow one to investigate the factors related to variability in adherence in different situations in individuals.

One qualitative study has described within-participants differences in ART adherence in HIV+ adult drug users (Wagner & Ryan, 2004). The authors found routine and changes to daily activities were associated with taking medication. However, in this research, psychological factors were not assessed. There may be particular situational psychological factors that also influence adherence, perhaps as potential mediators of the relationship between routine or changes to daily activity and adherence. These findings were in a specific subpopulation of HIV+ individuals: there may be differences in within-participants variation in routine or daily activities in younger participants.

Event-level design

It is also possible that there is difference in factors related to adherence within the individual according to specific contexts. Variation in actual or perceived barriers to or facilitators of adherence could be measured episodically, or relating to particular adherent or non-adherent events. Such a design may help to describe differences in situational ART adherence.

Only one study in adolescents describes situational factors that may influence adherence and non-adherence within young participants. MacDonell and colleagues recruited 82 suboptimally adherent (<90% in the past month, as measured by self-report) and 23 optimally adherent (>=90% in the past month) young people with behaviourally- and perinatally-infected HIV (Macdonell, Naar-King, Murphy, Parsons, & Huszti, 2011). They were asked to predict what might hypothetically tempt them not to take their medication in a variety of circumstances using a 14-item scale (α=0.93). Participants rated how tempted they might be to miss their ART on a scale of 1 – not at all tempted – to 5 – extremely tempted. The authors present descriptive statistics to demonstrate the degree of temptation per item within the whole sample. Independent t-tests were carried out between groups of optimal and suboptimal adherers to determine whether the hypothetical factors were related to non-adherence, as measured by the degree of endorsement in the suboptimal adherence sample. These results demonstrated disconnection between the expectation of which factors might be tempting and which factors were actually tempting. That is, young people endorsed different situations as most tempting not to adhere to ART than those that were statistically different between optimally

adherent and suboptimally adherent young people. This suggests a degree of unreliability in self-reporting related to hypothetical non-adherence. Therefore, an event-level design, where participants are required to report on an actual episode of adherence or non-adherence, may be beneficial.

An event-level/episodic design enables investigation of factors that relate to a given adherent or non-adherent episode. This promotes validity of remembering due to the structure and scaffolding of participant recall as related to a specific event. These designs have not been used in ART research, but have been the focus of other studies of health behaviour, including: alcohol and condom use in healthy adults (Leigh, 2002), substance misuse and sexual risk in men who have sex with men (Colfax et al., 2004), and marijuana use and condom use in adolescent women (Hensel, Stupiansky, Orr, & Fortenberry, 2011). Two investigations in Thalassaemia and smoking in relation to self-efficacy using event-level design have also been described above (Vosper et al., 2013; Van Zundert et al., 2011). Although event-level designs remain observational studies, they enable more robust inferences to be drawn about relationships between constructs and particular episodes.

Health Behaviour Theory

The majority of literature on medication adherence, particularly in paediatric populations, is atheoretical (Simoni et al., 2007). A PubMed search of HIV adherence literature based on theory (including: HIV + adherence + theory in the title/abstract, carried out on 18th February 2015) yields only 108 results versus over 6000 articles on HIV adherence without theoretical links. Even fewer studies are

published using theory to inform adherence research in children and young people (3). Of these three publications, one theory (Bronfenbrenner's Social Ecological Model) (Bronfenbrenner, 1977) was used to interpret qualitative interviews only (Coetzee, Kagee, & Bland, 2015). The remaining two studies were informed by the Information-Motivation-Behavioural Skills Model (Fisher & Fisher, 1992) and are discussed in further detail below (Dima et al., 2013; Rongkavilit et al., 2010); both were small, qualitative investigations. There are no studies to date that focus on ART adherence in PHIV+ young people that are informed by theory.

In the adult literature, theoretical models that are applied most often to ART adherence are those that incorporate multiple influences including self-efficacy, social support, problem solving and coping (Kaufman, Cornish, Zimmerman, & Johnson, 2014). Such models include: the Necessity Concern Framework (Horne, 2006), Social Cognitive Theory (Bandura, 1986) and the Information-Motivation-Behavioural Skills (IMB) model (Fisher & Fisher, 1992).

Necessity Concerns Framework

The Necessity Concerns Framework (Horne, 2006) identifies general attitudes towards medication alongside specific beliefs about particular medicines. According to this model, general beliefs are thought to impact on specific beliefs, which subsequently impact on adherence behaviour. The specific beliefs are grouped into beliefs about how necessary it is to take medication (necessity) and beliefs about risks associated with taking or not taking the medication (concerns), relating to side effects, for example. The Beliefs about Medicines Questionnaire (Horne, 2006) was

specifically developed to measure these constructs and has been used in a number of populations across conditions, with a specific version related to ART (Horne et al., 2007). In a randomised trial of ART, treatment adherence and beliefs about ART, low adherence (as measured by <95% self-reported adherence over 48 weeks or discontinuing the study) was associated with significant doubts about the necessity of ART and strong concerns about side effects. The concerns about side effects were diminished when participants were switched to a once daily ART regimen with no impact on viral load (Cooper et al., 2011). This may suggest that the concerns were less important than the ART regimen itself as related to adherence.

The Necessity Concern Framework primarily focuses on motivational constructs as antecedents to health behaviour, not necessarily in keeping with some of the empirical ART adherence literature which points to other determinants of adherence or non-adherence. The NCF may overlook the impact of personal adherence skills and self-efficacy, or the confidence to enact these skills. Post-motivation processes may also be important to enable motivation to be enacted in the form of adherence behaviour.

Social Cognitive Theory

Bandura's Social Cognitive Theory (SCT) (1986) departs from a primarily motivational model (such as the NCF) and proposes a reciprocal relationship between personal factors (including cognitive, affective, and biological), environmental factors and behaviour which interact to determine motivation and action. The model

emphasises the important influence of the social world and external and internal social reinforcement. It stresses observational learning, or witnessing and reproducing others' behaviour, as key to an individual's future actions.

This theory evolved from Social Learning Theory to explain how humans acquire and maintain behaviour within a social context. Self-efficacy, or the confidence one has to perform an action competently, is included in SCT. As such it was one of the first theories to highlight this as an important construct. In this model, self-efficacy is also influenced by individual and environmental factors. SCT has been applied to a number of health behaviours and interventions, including smoking cessation, weight management and contraceptive use (Maibach & Murphy, 1995; Strecher, DeVellis, Becker & Rosenstock, 1986).

Using SCT, Brown and colleagues (2013), investigated barriers to adherence in 116 HIV+ adults in a mid-sized city in northeastern USA. Self-reported suboptimal (<95%) ART adherence was associated with reduced ART adherence self-efficacy; fewer negative outcome expectancies for non-adherence, reduced perceived risk of ART non-adherence and reduced perceived need for ART. A logistic regression model controlling for age, gender, ethnicity, duration of ART and number of daily pills found suboptimal adherence was associated with lower levels of adherence self-efficacy, lower subjective beliefs about the importance of ART and a greater number of perceived acceptable missed doses, with a high goodness of fit ($p<0.001$). ART outcome expectancies, attitudes towards ART and perceived necessity of ART were

not associated with suboptimal adherence (Brown, Littlewood, & Vanable, 2013). This study highlights the importance of self-efficacy in ART adherence in adults, but did not find expected significant associations with outcome expectancy. This may suggest a strong influence of self-efficacy and a more variable influence of outcome expectancy that warrants further investigation.

Although SCT addresses the need for objective and perceived skills, normative social support and adequate information, it does not include normative beliefs or knowledge about a medication regime, which may be important for adherence behaviour. Furthermore, it has only rarely been used to investigate ART adherence and was not specifically designed for use in HIV+ populations.

The Information-Motivation-Behavioural Skills Model (IMB) (Fisher & Fisher, 1992)

IMB is a multivariate model informed by the Theory of Reasoned Action and the Theory of Planned Behaviour. This framework emerged directly from the HIV prevention literature. It has been applied to HIV-related risk behaviours, including promotion of contraception amongst adolescents, and has been adapted to be specific to ART adherence (Fisher, Fisher, Amico, & Harman, 2006). The adapted model draws on research at the individual level in an effort to improve understanding of the complex relationships in prescribing and adhering to ART medication regimens. It describes the relevant behavioural and psychological constructs in maintaining sufficient ART adherence in individuals with HIV under the categories of: information, or understanding of the regimen, side effects and personal theories (including misinformation) about the medication; motivation,

which encompasses both personal motivation, or outcome expectancies and their perceived importance, and social motivation, or the perception and importance of others' wishes in relation to ART adherence; and behavioural skill, incorporating objective skills in being able to take medication as well as perceived self-efficacy in using those skills (Fisher et al., 2014). The model also includes moderating variables including mental health issues, unstable living situation and current substance misuse (Amico, Barta, Konkle-Parker, & Fisher, 2009).

A diagrammatical representation of the IMB model can be found below (Figure 1) (Fisher, Amico, Fisher, & Harman, 2008). Solid line arrows indicate directional relationships between constructs. The main determinant of adherence is behavioural skill, which has been found to be related to medication adherence in multiple studies across cultures (Puerto Rico: Amico et al., 2005; Italy: Starace et al., 2006), across HIV populations in and out of clinic settings (Horvath, Smolenski, & Amico, 2014) and in other chronic health conditions such as diabetes (Mayberry & Osborn, 2014). Links between motivation and adherence are hypothesised to be mediated by behavioural skills. The information construct is not always found to be significant in tests of the model (Horvath et al., 2014).

Each of the IMB constructs might vary according to situation, making this model well suited to research of differences within individuals across contexts. In a study of condom use using the IMB model, changes in behavioural skill over time were

related to changes in condom use (Walsh, Senn, Scott-Sheldon, Vanable, & Carey, 2011).

This model has been applied to developing a computerised clinical intervention demonstrating significant improvements in ART medication adherence in a recent randomized control trial in HIV+ adults (Fisher et al., 2011) and to other interventions (Konkle-Parker, Amico, & McKinney, 2014) to promote HIV-prevention and adherence behaviours in HIV a variety of other chronic conditions (Chang, Choi, Kim, & Song, 2014).

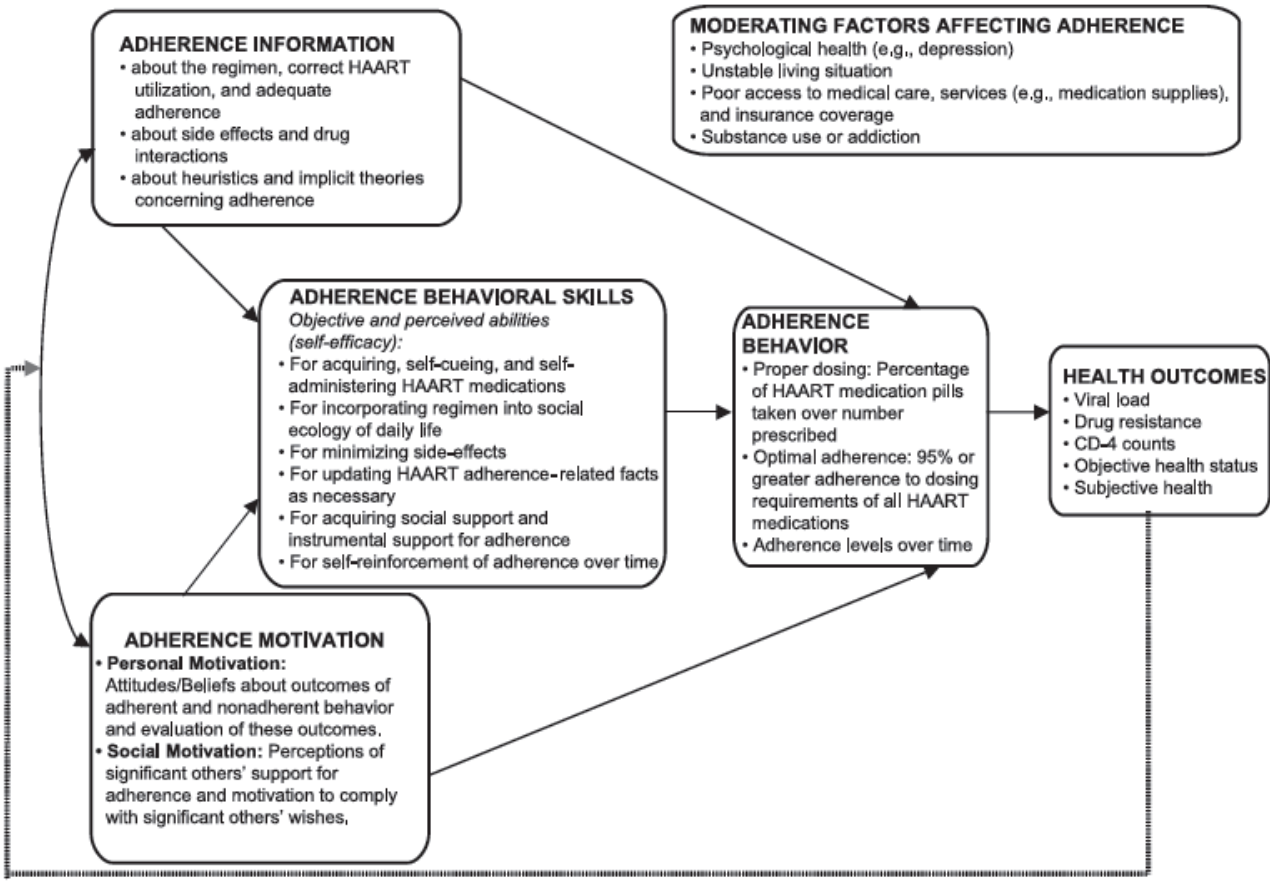

Figure 1. **The Information-Motivation-Behavioural Skills Model of ART Adherence (from Fisher, et al, 2006)**

In adherence research with HIV+ adolescents, the IMB model has only been applied in two qualitative studies: one investigation with BHIV+ Thai youth (Rongkavilit et al., 2010) and one with young Romanian individuals with long-term HIV+ status (nosocomically infected, acquired through contaminated blood transfusion or non-sterile medical equipment, at an early age) (Dima, Schweitzer, & Amico…, 2013) . Dima and colleagues held small, semi-structured focus-group discussions to which they invited small numbers of young patients (age 13-20) and healthcare professionals. Their interview structure broadly grouped questions into information, motivation, behavioural skills and general themes. They conducted thematic analysis to assess the relevance of the IMB model's concepts to their population and concluded that it was a valid theoretical framework on which to investigate facilitators of and barriers to medication adherence. The patient participants in this study were nosocomially infected at an early age, so do not correspond exactly to the PHIV+ population under investigation in this study. However, they are likely to share a number of characteristics due to the long duration of their infection. The researchers in Thailand were interested in investigating whether the IMB model would apply to youth living in a more collectivist culture (Rongkavilit, et al, 2010). They found support for all IMB constructs in their data. The motivation construct was particularly endorsed through statements regarding: the social influence of partners and other family members on adherence; a sense of responsibility to others; and belief in the health benefits of ART. The authors emphasise social motivation as key to adherence in their sample, however there appears to be a conflating influence of practical social support in their conclusions. That is, within

the IMB model, social motivation refers to the perception of having support to adhere to ART from others, not the actual presence or absence of others.

Research into individual differences, such as variation in adherence behaviour, must remain grounded in theory (Johnston & Johnston, 2013) . Furthermore, Fishbein argues that the role of behavioural sciences in managing HIV is to develop theory-driven interventions to promote health affirming and reduce risky behaviours (2000). There is a case for using the IMB model as a framework for the present study with a UK-based PHIV+ adolescent population investigating within-participant differences. No quantitative investigation of ART adherence factors in adolescents has used the IMB theory to inform the research. A quantitative approach allows one to look at the magnitude of relationships and comparisons between variables. A within-participant, event level design enables the study of factors that are related to specific episodes of individual variation in adherence behaviour.

Interventions to Promote Adherence

The clinical utility of understanding adherence behaviour is to inform intervention to improve and promote treatment adherence. A list of strategies that have been used with PHIV+ children and young people to promote ART adherence can be found in the table below (Agwu & Fairlie, 2013). Strategies are categorised into those that address medication barriers, patient-related factors and behavioural interventions. Few intervention studies focus on PHIV+ young people specifically. One recent trial combined financial incentives with motivational interviewing for a small sample

(n=11) of British PHIV+ 16-25 year olds with advanced disease (CD4 <200 cells/ µl) who had poor adherence and were transitioning from paediatric to adult services. There were improvements on viral load and CD4 count (Foster, McDonald, Frize, Ayers, & Fidler, 2014). This study was a small pilot with a subgroup of PHIV+ young people and it is not clear how successful this intervention would be in other adolescents with more inconsistent adherence. A second pilot project with PHIV+ young people in the USA combined group and individual behavioural therapy with the aim of improving HIV-related knowledge, disease management skills and reducing risky behaviours (Chandwani, Abramowitz, Koenig, Barnes, & D'Angelo, 2011). In their report, the authors describe only the acceptability of the intervention to the young people by attendance rates: there is no measure of adherence outcome. Other interventions have been tailored to particular HIV+ subpopulations, such as LGBT youth (Thurston et al., 2014).

There is no 'gold standard' intervention to address ART non-adherence in adolescents or adults (Agwu & Fairlie, 2013), nor do published guidelines specify exactly which strategies should be use to manage barriers to promote adherence (BHIVA, 2014). A number of systematic reviews have recently been published in relation to adherence interventions in HIV+ adults, children and adolescents (Arrivillaga, Martucci, Hoyos, & Arango, 2013; Bain-Brickley, Butler, Kennedy, & Rutherford, 2011; Chaiyachati et al., 2014). Such interventions are often multi-faceted and combine two or more components. Most often, these approaches include: education and/or general counselling, motivational interviewing, cognitive-

behavioural therapy, directly-observed therapy, financial incentives and social support, or treatment 'buddies' (Chandwani et al., 2011; Cooperman & Arnsten, 2005; Lyon et al., 2003; Mbuagbaw, Ye, & Thabane, 2012). However, many adherence interventions have no observable or sustained effect on treatment outcomes (Mathes, Pieper, Antoine, & Eikermann, 2013). In a systematic review of all published interventions for HIV+ young people only, just four met criteria for inclusion (randomised or non-randomised controlled trials of interventions to improve adherence to ART among children and adolescents (age ≤18 years), with ART adherence reported as an outcome). Of these four studies, no intervention resulted in significant or sustained change in ART adherence (Bain-Brickley et al., 2011). Many other studies neglect to measure adherence as a specific outcome of the intervention, or are observational in nature, and lack a control group.

The process of adherence is idiosyncratic: facilitators of or barriers to adherence may fluctuate; there may be a dynamic interaction between contextual and psychological factors (Buchanan et al., 2012; Reisner et al., 2009). Therefore an episodic within-participants investigation of determinants of adherent and non-adherent episodes is indicated as complementary to the existing literature on factors associated with between-participant, global adherence.

Table 1*: Strategies used to promote ART adherence in PHIV+ youth (Agwu & Fairlie, 2013)*

Strategy
Medication-related barriers
• Reduced pill burden (e.g. once daily/fixed-dose combinations)
• Palatable formulations (liquid, powder, crushing)
• Management of side effects
• Anti-nausea, anti-diarrhoeal agents
• Change timing of dosing (e.g. nighttime dosing)
• Regimen change
Patient-related factors
• Disclosure
• Counselling to deal with loss/trauma
• Treatment of concurrent psych diagnosis (e.g. anxiety, depression, substance abuse)
• Education about HIV and benefits of Cart
Behavioural interventions
• Motivational interviewing
• Counselling, support groups
• Life skills education with time-management and prioritization
• Parental/caregiver involvement
• Buddy systems
• Adherence clubs
• Peer motivators/educators
• Activity triggers (e.g. meals)
• Calendars
• Technological interventions (e.g. cell phone (calls or SMS texts, watches, beepers))
• Pill boxes
• Pharmacy clinic
• Directly observed therapy
Structural barriers
• Address barriers such as transportation, insurance, child care, clinic hours
• Education of clinic staff about cognitive and development stage of adolescence

Introduction to the study

This study focuses on situational behavioural and theoretically driven psychological factors and ART adherence in young people with PHIV+. This addresses the gap in the adherence literature concerning within-participant determinants of actual adherent or non-adherent events in this population.

The aims are to quantitatively explore psychological situational factors and episodes of adherence and non-adherence to ART. An event-level design is used to investigate specific adherent and non-adherent episodes. The study aims to investigate whether the relationship between psychological situational variables and adherence is consistent with the IMB model. Additional factors from previous studies are also investigated, including behavioural situational variables and forgetting.

Research questions

The main research questions for this study (consistent with the IMB model) are as follows:

1) Are there differences in levels of HIV adherence information between an episode of ART adherence and an episode of non-adherence?
2) Are there differences in levels of HIV adherence motivation between an episode of ART adherence and an episode of non-adherence?
3) Are there differences in levels of HIV adherence behavioural skill(s) between an episode of ART adherence and an episode of non-adherence?

4) Are there differences in situational emotional states between an episode of ART adherence and an episode of non-adherence?
5) Are there differences in situational street drug or alcohol use between an episode of ART adherence and an episode of non-adherence?

In addition, secondary to the above: are there differences in behavioural situational variables between an episode of adherence and an episode of non-adherence?

Method

Event-level design

An event-level design was used. The approach required collection of quantitative questionnaire data for the independent variables (described below) for separate episodes of adherence and non-adherence per participant. This within-participant design enabled static demographic variables (such as age, gender, ethnicity) to be controlled for (as they did not vary within individual).

The study had two components: a retrospective and a prospective component. Identical questionnaires were administered retrospectively and prospectively (see Appendix 13). The prospective part of the study aimed to limit possible recall bias in retrospective reporting. The questionnaire was constructed using elements of the Day Reconstruction Method to reduce recall bias of the retrospective report (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004). Situational behavioural variables were presented first, prior to any ratings of situational psychological states,

to enhance the detail of the episodic memory. These included the particular day of the adherent or non-adherent event, where the participant was at the time and who was with them at the time (discussed further below). These variables were under investigation as possible predictors of adherence or non-adherence, but served a dual function in orienting participants to the specific contextual details of the episode.

Within-participant variables

The dependent variable for both retrospective and prospective components was bivariate: adherent or non-adherent episode.

The main independent variables were chosen to be consistent with the IMB model (Fisher & Fisher, 1992):

- Information, or factors related to how knowledgeable young people felt about their ART regimen (Fisher et al., 2006). For this study, the information construct referred to the subjective level of knowledge young people possessed at the time of the scheduled dose and how knowledgeable they felt in taking their medication in the specific context at that time. Although level of knowledge does not change according to situation, different situations demand access to different aspects of information. For example, having not eaten or having consumed alcohol at the time of a dose may impact on the ways in which medication should be taken. Therefore, the type of information or knowledge required in relation to ART adherence may vary according to situation.

- Motivation, relating to personal and/or social motivation for taking medication at the time of the adherent/non-adherent episode. Personal motivation encompasses one's own attitudes towards or beliefs about the medicines and the outcomes of adhering or not adhering and the subjective importance of these outcomes. Social motivation involves the appraisal of others' beliefs about the individual taking medication as well as an evaluation of the importance of the other to the individual (Amico, Barta, Konkle-Parker, & Fisher, 2009).

- Behavioural skills, or the degree to which participants felt confident in their abilities to take their medication at the time of adherence or non-adherence as well as their actual level of skill in taking the medication. It was not possible to measure objective behavioural skills through self-report questionnaire. Therefore, this variable was operationalized as perceived behavioural skills only, which is consistent with the usual approach to IMB investigations (e.g. Dima, Schweitzer, & Amico…, 2013; Horvath, Smolenski, & Amico, 2014; Rongkavilit et al., 2010)

- Positive and negative affect, or situational emotional states. A lack of positive affect, or feelings of pleasurable engagement, enthusiasm and activity, is associated with depression in the tripartite model in adults, children and adolescents (Chorpita & Daleiden, 2002; Clark & Watson, 1991).

Negative affect also relates to states of mood and describes emotionally distressing states such as fear, sadness and guilt. Experience of negative affect is a shared component of both anxiety and depression; low positive affect is specific to depression. Depression and low mood have often been found to be associated with poor adherence to treatment in HIV and other chronic health conditions in adults and adolescents (Chandwani et al., 2012; Sheth et al., 2015; Taddeo et al., 2008; Uthman et al., 2014; Vasylyeva et al., 2013). Mental health is included as a moderator in the IMB model.

- Street drug and alcohol use. Use of substances has been linked with nonadherence in adults and teenagers with HIV (Dewing et al., 2015; Hosek, Harper, & Domanico, 2005). Substance use or addiction is included as a moderator in the IMB model.

Situational variables not included in the IMB model, that have been linked with adherence in several between-participants studies of adherence in PHIV+ young people (e.g. Chandwani et al., 2012; Kang, Delzell, Chhabra, & Oberdorfer, 2014; Mutwa et al., 2013)and HIV+ adults (e.g. Wagner & Ryan, 2004) were also investigated. These included where, when, and with whom the individual was at the time medication was due.

The extents to which a non-adherent dose was perceived to be due to forgetting and whether the adherent dose was perceived to be the young person's choice were also measured.

Sample

Adolescents and Adults Living with Perinatal HIV (AALPHI) Study

The Adolescents and Adults Living with Perinatal HIV (AALPHI) project is a prospective cohort study of young people living with or affected by perinatal HIV carried out in collaboration with the Medical Research Council Clinical Trials Unit (http://www.ctu.mrc.ac.uk/our_research/research_areas/hiv/studies/aalphi/). The study has recruited two groups, one group of PHIV+ young people who have been followed up in the Collaborative HIV Paediatric Study (CHIPS) project through childhood; the second (control) group are HIV negative young people who have a parent, sibling or friend with HIV.

The AALPHI project follows young people from the CHIPS cohort with the aim of describing the transitional period from paediatric to adult care. Participants are interviewed to investigate the impact of prolonged ART and growing up with HIV in domains of physical health and development as well as neurocognitive function and psychosocial issues. Follow up interviews take place yearly for a planned period of five years. At the time of this project, AALPHI was in the second year of data collection.

AALPHI interviews are carried out by three research nurses with experience in paediatric and/or HIV care under the supervision of the principal investigator, an epidemiologist. The nurses supported the current project in approaching and introducing the study to eligible young people at the recruitment sites at the same time as organising the second-year AALPHI follow up interviews.

AALPHI Participants

Young people were recruited to participate in the AALPHI study via 20 clinics and voluntary organisations across the UK, of which seven were outside of London. Inclusion criteria for PHIV+ young people to the AALPHI study included:

1. History of paediatric care in the UK
2. Perinatally infected/acquired HIV
3. At least 13 years of age and not older than 21 years at the time of enrolment to AALPHI
4. Living in the UK for greater than 6 months
5. Able to give informed consent or assent
6. Able to speak and understand English
7. Willing to be followed up annually for the duration of the study

Young people outside this age range or who acquired HIV behaviourally were excluded from AALPHI. PHIV+ young people who had been aware of their HIV status for six months or less were also excluded.

Seventy-three percent of the total AALPHI sample were recruited from London sites. The median age at time of enrolment to the study was 16 (IQR=15-18) and 41% of

the sample are male. Participants of black ethnicity comprised 86% of the sample. Almost all young people in AALPHI are single (99.7%) and 1% are parents. Of the total sample, 93% live with their parent or parents. The median age of paediatric disclosure (when the young person was told their HIV status) in the total AALPHI sample is 12 (IQR 11-13). Eighty-eight percent of the total AALPHI sample were currently taking ART, comprising 259 people. Of these 259, 32% missed two or more days in a row in the month prior to the interview (n=83).

Sample size calculation

The target sample size was estimated using the bivariate analyses to inform the a-priori power calculation. No comparable within-participant studies have been conducted for ART adherence; therefore two comparable studies using similar methodology in different health behaviours were selected for calculating effect size. Both studies measured episodic differences in self-efficacy and outcome expectancies in health behaviours. Self-efficacy is equivalent to the behavioural skills construct in the present study; outcome expectancies is similar to personal motivation.

The first study, an investigation of within-participant differences in medication adherence in Thalassaemia (Vosper, Evangeli, Porter, & Shah, 2013), found an effect size of d=0.41 (Cohen, 1992) for outcome expectancies and d=1.09 for self-efficacy. The second study measured within-participant variation in self-efficacy and outcome expectancies related to smoking behaviour between relapse and no relapse days

(Gwaltney, Shiffman, Balabanis, & Paty, 2005). The difference between self-efficacy between relapse and no relapse had an effect size of d=0.62 (Cohen, 1992). For outcome expectancies, Cohen's d was calculated as d=0.75.

The mean effect sizes from these studies for each variable were calculated at 0.58 for outcome expectancies and 0.86 for self-efficacy. These figures were used in the a-priori power calculations. Using a paired two-tailed t-test for calculating the mean scores on behavioural skills between adherent and non-adherent episodes and estimating the effect size of 0.86, power statistic β=0.8 and alpha level p=0.05, the minimum number of participants required is n=20 (as calculated in G*Power). For personal motivation, using an effect size of 0.58, power statistic β=0.8 and alpha level p=0.05, the minimum number of participants required is n=41.

Recruitment sites

It was not possible to recruit from all AALPHI sites for the present study. A sub-sample of participants were recruited from two London hospitals, one London voluntary-sector organisation and one clinic outside of London. Of the London sites, one hospital held two clinics: one paediatric and one transitional clinic from which participants were recruited. The second London hospital had a smaller number of patients with a single transition clinic from which participants were recruited.

The voluntary-sector organisation was based in central London and provides a supportive social space for young people age 13+ once a week. Young people already recruited to AALPHI who attended this centre were approached to take part

in this study in between the workshops and events at the centre, so as not to interfere with their time. Young people recruited outside of London all attended a regional hospital clinic supported by both adult and paediatric services. No young people attended nor were recruited from adult-only clinics.

Inclusion/Exclusion criteria

Inclusion criteria for the current study were based on those from the larger AALPHI: participants must have been enrolled in AALPHI to be eligible for this project. Additionally, participants were only recruited from the sites mentioned above. The final inclusion criteria for this project were for the young people to have been currently taking ART medication and the ability to recall one adherent and one non-adherent event in the preceding two months.

A missed dose or non-adherent event in the last two months was assessed by asking participants if they could remember a particular episode where they did not take their medication as prescribed, i.e. a dose was skipped altogether for that day or there was a very significant delay from when they were supposed to take their medication. The time frame of two months was decided upon to balance recall issues with normalising adherence. This is the same period used successful in a previous study using this methodology in adults with Thalassaemia (Vosper et al., 2013). In this study, the mean number of days of the non-adherent event prior to measurement was 10 days; of the adherent event, the mean number of days was 1.3. This suggests that most people were reporting both episodes within the previous two weeks.

Participants without capacity to consent for themselves were excluded, as were young people without a good understanding of written and spoken English (a good understanding defined as: able to understand verbal instructions and capable of reading the information sheet and questionnaire independently). Young people with significant cognitive impairment were not eligible for the study.

Sampling procedure

A systematic sampling method was used to reduce bias in recruitment. During the study period, clinic lists for each of the London hospital sites were obtained. AALPHI research nurses identified AALPHI participants from each list. Those who were not prescribed ART were removed from the list of whom to approach. All remaining eligible patients were approached to invite them to take part in the study. At the voluntary organisation, a list of young people who were expected to attend the following evening session was sent to the AALPHI research nurse, who identified AALPHI participants. These young people were then approached if they attended and were not engaged in workshops that evening. The regional hospital (outside London) was added to the list of recruitment sites towards the end of the recruitment period. Therefore, all AALPHI participants between December 2014 and April 2015 were approached to participate. A total of 36 young people were invited to participate, of whom 29 completed the retrospective questionnaires for both episodes. A total of six people completed at least one prospective questionnaire (n=6 for adherent episode; n=4 for non-adherent episode), of whom four completed prospective questionnaires for both episodes.

Characteristics of the sample

Participants' baseline data from enrolment into AALPHI were collated to characterise the sample. Demographic information, including age, gender, country of birth and ethnicity of the 29 recruited participants are presented in the table below.

Table 2*: Demographic information*

Variable		
Age	Mean	17.3
	Median	17
	SD	1.99
	Range	14-22
Gender	Male	12 (41%)
	Female	17 (59%)
Birthplace	UK	8
	Zimbabwe	6
	South Africa	3
	Uganda	3
	Tanzania	2
	Zambia	2
	Ethiopia	1
	Ivory Coast	1
	Rwanda	1
	Malawi	1
	Norway	1
Ethnicity	Black African	25 (86%)
	Black Caribbean	1
	Mixed: White & Black African	2
	Prefer not to say	1

The gender split in the current sample matches that of the wider AALPHI population (41% male). The median age of participants matches the AALPHI population (median age at enrolment 16, second year of project = 17). The percentage of participants of Black African ethnicity exactly matches the AALPHI group. This suggests the sampling strategy was successful in recruiting a demographically representative group from AALPHI.

Table 3, below, presents descriptive characteristics of the sample at entry into AALPHI, including their ART regimen frequency, a subjective rating of their overall ART adherence, the number of people they had disclosed their HIV status to outside their family, whether they had ever been referred to CAMHS and their current alcohol use.

Table 3*: Descriptive information*

Variable			Frequencies
Medication	**ART once daily**		24
	ART twice daily		1
	Missing		4
Adherence	**Subjective rating of**	**Excellent**	12
	overall adherence	**Good**	11
		Not so good	2
		Missing	4
HIV Disclosure	**Number of people**	**10+**	3
	disclosed to	**5-9**	1
		3-4	1
		1-2	10
		0	11
		Missing	3
Referred to	**Yes**		1
CAMHS?	**No**		24
	Missing		4
Alcohol use	**Never**		18
	Monthly or less		6
	2-4 times/month		2
	4+ times/week		2
	missing		1

Measures

Questionnaire Development

Adaptation of The LifeWindows Information Motivation Behavioural Skills ART Adherence Questionnaire (LW-IMB-AAQ) (The LifeWindows Project Team, 2006)

The LifeWindows Information Motivation Behavioural Skills ART Adherence Questionnaire (LW-IMB-AAQ) (The LifeWindows Project Team, 2006) is a 33-item scale measuring IMB-related adherence barriers (Appendix 8). The questionnaire was developed for computerised administration as part of a computerised adherence intervention for adults living with HIV in clinical care settings in the USA (Fisher, et al, 2011). The measure was designed with two primary functions: to quantify strengths and needs in ART related information, motivation and behavioural skills; and to identify potential specific deficits in one or more of these areas for targeted and effective intervention.

The LW-IMB-AAQ comprises three subscales to measure each of the IMB constructs. A nine-item subscale measures information with internal consistency of α=0.59 (LifeWindows Project Team, 2006). The authors explain the low reliability due to the variety of information about diverse aspects of ART regimen; higher levels of internal consistency would not be expected. Ten items, seven of which measure personal motivation and three measure social motivation, measure the overall motivation construct (α=0.70). The remaining 14 items form the behavioural skills-subscale with excellent internal consistency α=0.90. The questionnaire has been adopted for use

in out-of-clinic settings in the US (Horvath et al., 2014) and cross-culturally in Argentina (Torija, Vázquez, Montijo, & Romo, 2015) and South Africa (Dewing et al., 2015).

The LW-IMB-AAQ appears not to have been used in research with adolescents, although the authors suggest that the questions are likely generalizable to other HIV+ populations (Fisher, et al, 2006).

Process of Adaptation

The LW-IMBQ-AAQ required adaptation because the wording was unsuitable for referring to specific episodes of adherence or nonadherence; no other measures were available. When adapting the measure for use in the present study, it was important to consider the original context of its development. The LW-IMB-AAQ was developed for adults, in clinical care setting and as a measure of global adherence. Therefore, it was necessary to consider what amendments were necessary to make the tool applicable to young people and relevant to particular episodes of adherence and non-adherence.

Advice was sought from the one of the original authors of the LW-IMB-AAQ prior to and throughout the adaptation process (Amico, personal communication). The first step taken was to remove items that would not be relevant situationally or apply to the target group. This was done prior to piloting by the author and supervisors. The proposed omitted items were later presented to a focus group made up of the target

population (discussed below) who corroborated that these items had not been erroneously excluded.

The second step was to remove items that did not make conceptual sense situationally. Some items measured static constructs or attitudes, such as "As long as I'm feeling healthy, skipping my HIV medications from time to time was OK". Three information items, seven motivation items and ten behavioural skills items remained after this process.

Additional items were added to the subscales based on factors found to be significant in between-participant ART adherence studies in PHIV+ (Agwu & Fairlie, 2013; Macdonell, Naar-King, Murphy, Parsons, & Huszti, 2011; Rudy, Murphy, Harris, Muenz, & Ellen, 2010), such as perception of effectiveness of ART, or outcome expectancies, (e.g. "I thought my medication was helping").

Questions relating to complexity and burden of regimen did not appear in the LW-IMB-AAQ, but has been suggested as an important determinant of adherence (Nachega et al., 2014). Therefore, an additional item was added to the Information subscale, in terms of participants' understanding of their specific regimen ("I understood what medication to take"). An extra item was added to the personal motivation subscale relating to perceptions of the size, taste or amount of medication. One item was added to the behavioural skills subscale to measure confidence in adhering to the regimen correctly.

A component of outcome expectancy, perceived effectiveness of medication, was neglected in the LW-IMB-AAQ. Therefore, two items measuring this were added to the personal motivation subscale.

A link between ease of access to medications and situational adherence has been found in adults with HIV (Wagner & Ryan, 2004) and Thalassaemia (Vosper, Evangeli, Porter, & Shah, 2013). The LW-IMB-AAQ asks only about prescription refills rather than situational access to medication, therefore this item was amended.

A question about confidence to remember ART was included from the LW-IMB-AAQ, but there was no question about degree of forgetting or volitional adherence (or choosing to take medication). Extra items were added to the non-adherent episode questionnaire and adherent questionnaire, respectively: "I completely forgot" was rated in relation to non-adherence; "Taking the medication was my choice" was rated in relation to adherence. The final questionnaire can be found in Appendix 13.

Wording

In the design of a questionnaire, it is necessary to strike a balance between being comprehensive and not too onerous to complete, therefore careful attention must be paid to the wording. Wording and phrasing changes were made subsequent to focus group consultation. However, a consistent wording format was mostly followed. For Information, questions began with "I knew…" or "I understood…"; for

Personal motivation, questions mostly began with "I thought…"; for Behavioural Skills, questions mostly began with "I felt/was confident…"

Focus Group Piloting

A group of 12 young people from the Children's HIV Association (CHIVA) were approached to pilot the adapted questionnaire; all were PHIV+ and were prescribed ART. Each young person was given a copy of the draft questionnaire to look at and asked to feedback in terms of clarity and understanding of each item, relevance, comprehensiveness and feasibility of the questionnaire. The pilot group were also asked about their views on the layout and style of response options. A "think aloud" technique was used, whereby participants were asked to verbalise their thoughts around how they would answer the question and their thoughts about how relevant the question was to their own medication adherence (Ericsson & Fox, 2011).

Administration Format

The questionnaire was available in both paper and pencil and online format. The original questionnaire was administered in a computerised format; therefore this is in keeping with the original mode of administration.

The standard software of the Royal Holloway University of London Psychology department was used for the online version of the questionnaire (SelectSurveyASP Advanced [version 8.6.4]). The URL hyperlinks to the questionnaire were exceptionally long, therefore would have been prone to error when typing or copying into an internet browser. Therefore the links to the questionnaire were

routed through tinyurl.com to simplify the online procedure. This is an online tool for condensing long URL links into a more useable format.

Length & Order of Questions

The relationship between response rate and length of questionnaire was a concern for this study. Participant boredom and fatigue induced by overly lengthy questionnaires may impact on the validity of responses. Participants may employ particular response strategies, be subject to learning effects, or be careless in questionnaire completion (Warnecke et al., 1997). Learning effects would reduce variance of responses and response strategy would increase variance of responses. These would cause difficulties with statistical analysis due to non-random patterns of variance.

In the current study, consideration was given to the number of questions and how lengthy the questionnaire would appear in each format. The paper version was kept to four sides of paper per episode and the online version was limited to a total 10 screens to avoid over-burdening participants.

Single Question Survey Response & Scales

To measure a psychological construct most reliably, it is recommended that a number of items representing this construct are included in the questionnaire and the responses rated on a summative scale (Oppenheim, 1992). Therefore, psychological variables including the IMB constructs, positive and negative affect (described below), feeling ill, forgetting and choice were rated on a five-point Likert scale, where responses indicated to what extent participants agreed or disagreed

with the statement. Behavioural situational variables (described below) were measured with single item survey responses.

Final Questionnaire Items

The introduction to the questionnaire asked participants to think about the time when they did or did not (depending on episode) take their medication, and answer the questions based on how they felt and what they thought at that time.

Situational Context

Situational non-adherence in adult patients who are prescribed ART has been found to be related to daily activities (Wagner & Ryan, 2004), as discussed in the Introduction. A number of questions with categorical responses were asked in relation to each episode, which covered:

- Day of the week
- Whether another person was there to remind about the medication (yes or no)
- Routine (if usual day or routine different to normal due to planned or unplanned activity)
- Location (if at home; a friend's house; partner's house; a public place such as work, school or college; a family member's house)
- Whether other people were present and, if so, who (alone; with friend; with partner; with family; with acquaintance; with work colleague)

- Whether street drugs or alcohol were used around the time of medication (yes or no).

IMB Constructs

The IMB constructs were measured by scale questions and rated on a five point Likert scale, in keeping with the LW-IMB-AAQ. Each item was introduced with "At the time: (please tick one)" and presented as a statement, such as "I knew the correct way to take my medicines". Responses ranged from 'Strongly Disagree' to 'Strongly Agree'.

Four items measuring situational Information were included in the final questionnaire. Ten items, relating to personal and social motivation, comprised the motivation scale. Subjective behavioural skill was measured by eight items.

Mood

Adapted Positive and Negative Affect Schedule (PANAS) – 10 item Children's Version

The original Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) was developed as a tool to discriminate between symptoms of anxiety and depression in adults. It was subsequently adapted for use in children and adolescents (Laurent et al., 1999) resulting in a 27 item self-report measure comprising two subscales of positive and negative affect.

Given the importance of minimising participant burden in the current questionnaire, a concise measure of positive and negative affect was required. The PANAS-Child

version has recently been adapted to a 10 item scale (Ebesutani, Regan, Smith, & Reise, 2012) using Item Response Theory (IRT) (Thomas, 2011). IRT is a psychometric approach that focuses on individual items to estimate a value of a construct, rather than an observed total as an estimate of a true test score (as would be the case in Classical Test Theory). This approach enables scales to be shortened without compromising accuracy. In a study of IRT applied to the PANAS-C, questionnaire items were reduced to 5 per scale without compromising the psychometric value of the tool. There were higher inter-item correlations in the shortened version, indicating a slightly less broad measure of both positive and negative affect, relative to the original measure. However, good internal consistency remained for both positive affect (0.85) and negative affect (0.82), divergent validity was not significantly different from the original scales and discriminant validity for specific mood disorders was good (as tested on a mental health clinic-based sample) (Ebesutani et al., 2012). Therefore, the shortened scale was chosen over other available measures due to its brevity and adaptability to an event-level design. In the current study, the internal reliability for both positive and negative scales between episode can be found in the table below.

Table 4: ***Cronbach's alpha reliability by subscale (standard 5 item)***

Episode	**Positive Affect**	**Negative Affect**
Non-adherent	.94	.93
Adherent	.91	.86

An additional four negative affect items were suggested in the piloting stage by the focus group. Although the PANAS-C short form is a standardised measure, it has not been validated in the PHIV+ population. Therefore, it may be that the constructs vary between populations. As such, focus group participants were asked whether there were other mood states that were present at the time of scheduled medication times (not covered in the PANAS-C). The following mood states were elicited: blamed, helpless, out of control and weak. To avoid bias towards negative affect items (with 9 negative items and 5 positive affect items), an additional four positive affect items were included to the questionnaire, derived from a critique of the PANAS (Peterson et al., 2013). These items were: calm, content, at ease and satisfied and measured the non-activated component of positive affect.

Participants were asked to rate the degree to which they felt each emotion at the time of their adherent or non-adherent event. The items were introduced with: How did you feel when it was time to take your medication?

Intention and volition

One item measured forgetting for the non-adherent episode. One item measured degree of personal choice in taking medication for the adherent episode. These were rated on the same five-point Likert scale, presented with the IMB items.

Somatic symptoms

Feeling ill at the time when the ART dose was due was also measured on the five-point Likert scale with the IMB items. This was included for both episodes.

Study Procedure

A diagram of the study procedure can be found below.

Participants enrolled in AALPHI were identified from clinic lists. All those who attended the clinic were approached either by a member of their clinical team or an AALPHI research nurse to inform them of the study. Interested and eligible young people were given paper information sheets by either the AALPHI research nurse or the author. Occasional non-adherence was normalised ("We know that sometimes it might be easier or more difficult to take medication and it is not uncommon for young people to occasionally miss a dose"), and participants were made aware that the information or their choice to participate or not would not be fed back to their clinical team.

The same procedure was followed for the non-clinic voluntary sector site: AALPHI participants were identified from a list of who was due to attend that evening. Those young people who were available for some part of the evening were approached by a volunteer or research nurse to introduce the study; young people who were engaged in other activities were not approached.

Young people who wished to participate were consented by the author or research nurse and given the option to consent and complete their questionnaire on paper or online. Online consenting was carried out in accordance with the BPS guidelines for internet mediated research (British Psychological Society, 2013). Participants were allocated a unique study number linked to their date of birth to maintain

confidentiality and anonymity of responses. The research nurses kept a record of which AALPHI participants had completed this study on the main AALPHI database. Fifteen participants completed a pen & paper version of the questionnaire, with the remainder online. Paper questionnaires were scanned and saved to an encrypted USB storage device. Online data was downloaded from the survey software and stored on the same encrypted USB device. The order of questionnaires was counter-balanced to control for order effects and 14 participants completed the adherent episode first. Participants were given a £10 voucher for taking part.

Prospective questionnaires

Following the completion of the retrospective questionnaire, participants were given the choice to enrol in the second half of the study: to receive SMS messages every three days to remind them to complete the questionnaire again, once after a non-adherent event and once after an adherent event. Participants had been informed of the two-part nature of the study during the consenting process, but were reminded of the second part and given the choice to opt out. Twenty-two participants chose to participate in this part of the study and were given a link to the online questionnaire with their unique study number to login to the survey. Participants were made aware that they could opt-out of the messaging at any time and were instructed on how to do so.

SMS reminders

SMS messages were sent via RedOxygen, a web-based service, which allowed scheduled reminders to be sent (RedOxygen Pty. Ltd., Brisbane, Queensland, Australia). This service has been used in other prospective research of health

behaviours (e.g. Berkman, Dickenson, Falk, & Lieberman, 2011). The URL links to each questionnaire (separate for each episode to avoid confusion) were sent via SMS. In keeping with the terms of use, whom the message was from (RHUL Research Project) and how to opt out of messages (Reply: "Stop" to opt out) was included in the SMS. Three people opted out of messaging, evidence by "failure to send" reports from the software.

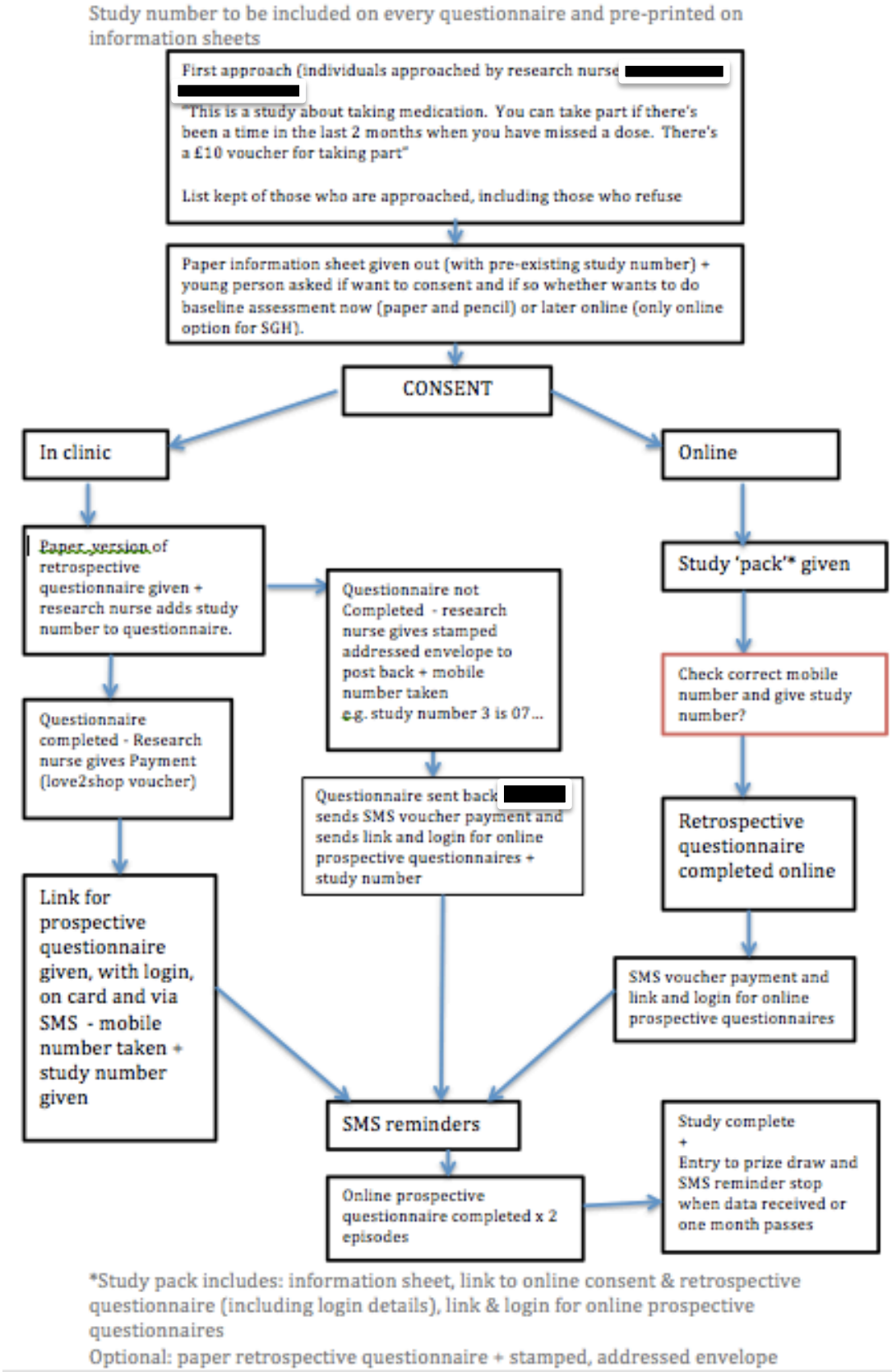

***Figure 2*: Study Procedure**

Ethics and Ethical Issues

This study was granted NHS approval by Berkshire B Ethics Committee. The study also received ethical approval from Royal Holloway University of London Psychology Departmental Ethics Committee (for approval letters, see Appendix 1-4). An amendment was submitted to adjust the upper age limit from 21 to 22, accounting for the age at which young people were initially enrolled in AALPHI, and to add the regional out of London hospital.

Research and Development approval was obtained for each NHS hospital site.

Analysis

Analysis was carried out in SPSS Statistics, version 21 (IBM Corp, 2012). Additional investigation of multivariate analysis assumptions took place in STATA IC version 11 (StataCorp, 2009).

Bivariate

Planned bivariate comparisons were conducted between responses for adherent and non-adherent episodes. Variables that met assumptions for parametric statistics were analysed using paired-samples t-tests.

Categorical variables between episodes were compared using McNemar's chi square tests.

Multivariate

Conditional logistic regression was used to explore associations between more than one independent variables and the dependent variable (adherent/non-adherent

episode). This was carried out as Cox regression in SPSS, due to a lack of conditional logistic regression function in this software. This model was selected because the dependent variable was binary (adherent versus non adherent event). It would have been inappropriate to use binary logistic regression because the observations were not independent. For case-control studies, or related observations, conditional logistic regression is the most appropriate multivariate model (Field, 2014).

Significance (as measured by a p-value >0.05) on the bivariate analysis and relevance to the IMB model were used to select the variables for inclusion in the regression model. The number of variables in the model was restricted due to power considerations. The model could support just two predictors because 29 participants were recruited (following the guidance of 10 cases per predictor (Tabachnik & Fidel, 2006).

Missing data

Missing data was omitted, not replaced with mean values. For the inferential analysis, missing observations were omitted on a pairwise basis.

Results

Retrospective Data

Twenty-nine participants completed the measures for both adherent and non-adherent episodes.

Categorical Variables: Data screening, Exploration and Grouping

Table 5, below, presents the frequencies of responses for non-adherent and adherent episode for the categorical variables. Due to small cell sizes for some categories, the following variables were grouped into dichotomous categories: with whom the adherent or non-adherent episode occurred (alone or with someone else), daily routine (the same as or different to normal), location at the time (at home or elsewhere) and day of the week for each episode (Monday to Thursday and Friday to Sunday). Additional categorical variables included in Table 5, below, are: whether there was a person to remind about the medication and whether there was substance use at the time of the episode.

Table 5: ***Categorical variables between adherent and non-adherent episodes***

Variable		**Non-adherent episode (frequencies)**		**Adherent episode (frequencies)**	
N (sample size)	29				
Weekday	Monday	4	*Mon-Thurs*	8	*Mon-Thurs*
	Tuesday	1	*11*	8	*22*
	Wednesday	5		2	
	Thursday	1		4	
	Friday	5	*Fri-Sun*	2	*Fri-Sun*
	Saturday	9	*16*	2	*5*
	Sunday	2		1	
	Missing	*2*		*2*	
Routine	Normal	12	*Same*	24	*Same*
			12		*24*
	Unexpected	8	*Different*	2	*Different*
	Planned	7	*15*	2	*4*
	Missing	*2*		*1*	
Location	At home	15	*At home*	25	*At home*
			15		*25*
	Friend's home	8	*Not at home*	0	*Not at home*
			14		*3*
	Public place	4		2	
	Family home	2		1	
	Missing	*0*		*1*	

Who with at time of dose/missed dose	Alone	8	*Alone 8*	12	*Alone 12*
	Friend	10	*Not alone 21*	0	*Not alone 16*
	Partner	2		0	
	Family	9		16	
	Missing	*0*		*1*	
Someone there to remind you	Yes	11		9	
	No	18		19	
	Missing	*0*		*1*	
Substance use	Yes	4		2	
	No	25		26	
	Missing	*0*		*1*	

Reliability of the IMB subscales

The reliability of the IMB subscales in the measure was particularly important in this study, as the items were adapted from an existing measure. Internal consistency (measured by Cronbach's alpha) was calculated for each subscale in the IMB model for each of the episodes. The non-adherent information subscale alpha was 0.98 and 0.71 for the adherent episode. The motivation subscale alpha was 0.79 for the non-adherent episode and 0.76 for the adherent episode. For the non-adherent episode, behavioural skills alpha was 0.88 and for the adherent episode alpha was 0.83. Each of these statistics indicates acceptable reliability (Field, 2014).

Reliability analysis in SPSS calculates the correlation of each individual scale item to the total scale and the Cronbach's alpha if any one item is removed. This analysis was conducted to assess whether the adapted subscales could be refined to improve their psychometric properties. For the motivation subscale, the Cronbach's alpha improved from 0.79 to 0.85 for the non-adherent episode and 0.76 to 0.87 for the adherent episode if items 8 and 14 were dropped. The item-total correlations for these items were low. On further investigation, the two items differed from the remaining items in the subscale. Item 8 ("People around me that I care about were supportive about my medication") was the only social motivation item, whereas the other items related to personal motivation. The IMB model separates out these two components of motivation; therefore it was decided to investigate this social motivation item separately. Item 14 ("I was bothered by the size, taste or amount of medication") was a personal motivation item that was added from the service user consultation. Given its poor correlation to the subscale total, the increase in the Cronbach's alpha when the item was deleted and the fact it was not in the original measure, the item was dropped from the analysis entirely. An eight-item Personal Motivation scale was used for analysis (α=0.85, non-adherent episode; α=0.87, adherent episode). The remaining items on each of the subscales were highly correlated (>0.5) to the respective totals for behavioural skills and information. There were no items that would have improved the reliability by being dropped on these subscales.

Continuous variables: Data screening and descriptive statistics

The distributions of the continuous variables were tested for skew and kurtosis to determine whether normality could be assumed and if the data could be analysed with parametric statistics. In paired t-test analysis (which was planned), it is the distribution of the difference between matched scores that must satisfy the normality assumption, rather than the distribution of the individual variable scores (Field, 2014; Field, personal communication). Data for both non-adherent and adherent episodes were investigated as well as the differences between matched variables are presented in Table 6, below.

Table 6: ***Within-participant descriptive data for IMB variables per episode***

Variable (minimum-maximum score)	**Episode**	**Median (IQR)**	**Mean**	**SD**
Information (4-20)	Non-adherent	20 (17-20)	18.04	3.64
	Adherent	20 (18-20)	19.04	1.64
	Difference		*-.96*	*4.40*
Personal Motivation (8-40)	Non-adherent	21 (12-28)	21.14	8.59
	Adherent	22 (16-27)	21.54	8.06
	Difference		*-.33*	*5.99*
Social Motivation (1-5)	Non-adherent	3 (1-3)	2.52	1.33
	Adherent	1.5 (1-3)	2	1.28
	Difference		*-.54*	*1.48*
Behavioural Skills (10-50)	Non-adherent	29.5 (23-37)	29.75	9.52
	Adherent	39.5 (32-42)	37.92	7.29
	Difference		*-7.92*	*8.16*

With the exception of Information, all variables were normally distributed as determined by skew and kurtosis z scores <3.29 (Field, 2014). The Information

variable was negatively skewed, therefore this variable was transformed. Reverse-Log transformation successfully achieved a normal distribution (skew: z=-1.46, kurtosis: z=1.31). Following this transformation, there were no univariate outliers. The additional items measuring positive and negative affect (4 positive, 4 negative) were investigated separately to the standard 10 PANAS-C items. Descriptive statistics for the affective variables and the somatic item ("I felt ill") between episodes are presented below. None of these variables violated the assumption of normality, except for 'helpless', which was log-transformed from a positive skew to a normal distribution.

Table 7*: Descriptive statistics for somatic and affective variables*

Variable (minimum-maximum score)	**Episode**	**Mean (SD)**	**Range**	**Mean Difference (SD)**
PANAS-C 5 item Positive Affect (5-25)	Non-adherent	8.55 (4.55)	5-21	3.33 (5.72)
	Adherent	12.15 (6.02)	5-25	
PANAS-C 5 item Negative Affect (5-25)	Non-adherent	11.34 (5.97)	5-25	2.00 (5.67)
	Adherent	8.96 (5.25)	5-23	
Somatic symptoms "I felt ill" (1-5)	Non-adherent	2.52 (1.37)	1-5	0.08 (0.00)
	Adherent	2.54 (1.38)	1-5	
Blamed (1-5)	Non-adherent	2.17 (1.39)	1-5	0.85 (1.41)
	Adherent	1.41 (0.80)	1-3	
Weak (1-5)	Non-adherent	2.10 (1.21)	1-5	0.15 (0.91)
	Adherent	2.00 (1.44)	1-5	
Helpless	Non-adherent	2.17	1-5	0.35

		(1.47)		(1.06)
(1-5)	Adherent	1.77	1-4	
		(1.07)		
Out of control	Non-adherent	2.21	1-5	0.33
(1-5)		(1.40)		(1.04)
	Adherent	1.93	1-5	
		(1.36)		
Calm	Non-adherent	2.34	1-5	0.89
(1-5)		(1.32)		(1.76)
	Adherent	3.33	1-5	
		(1.49)		
At ease	Non-adherent	2.28	1-5	0.70
(1-5)		(1.31)		(1.54)
	Adherent	3.07	1-5	
		(1.54)		
Content	Non-adherent	2.14	1-5	0.63
(1-5)		(1.19)		(1.42)
	Adherent	2.85	1-5	
		(1.43)		
Satisfied	Non-adherent	2.17	1-5	0.74
(1-5)		(1.34)		(1.60)
	Adherent	3.00	1-5	
		(1.54)		

Two items relating to non-intentional and volitional adherence were included for the separate adherent and non-adherent episodes, rated on the same five-point Likert scale from 1 – Strongly Disagree to 5 – Strongly Agree. Reponses on these variables were normally distributed as determined by skew and kurtosis z scores <3.29 (Field, 2014). The median rating of "I forgot" for the non-adherent episode was 4 (IQR=2.25-5). The median rating of choice for the adherent episode was 5 (IQR 3.75-5).

Exploratory bivariate analysis

Paired samples bivariate analysis of the potential differences between adherent and non-adherent episodes was carried out for the variables relating to the secondary research questions. Potential differences on behavioural situational variables and somatic symptoms (measured by "I felt ill") between adherent and non-adherent episodes were tested.

Paired t-tests were used for the continuous variables and McNemar's Chi-Square analyses (using Fisher's exact estimates for expected frequencies less than 5) for the categorical variables. McNemar's tests for the difference between divergent pairs (Altman, 1991). The McNemar's statistic and Cramer's phi (as a measure of effect size) were calculated manually using the following formulae (Nandy, 2012):

$$\chi^2 = \frac{(c-b)2}{c+b}$$

$$\varphi = \sqrt{\frac{\chi 2}{N(k-1)}}$$

Cramer's phi values for 2x2 contingency tables (as below) indicate effect sizes as follows: .10 – small; .30 – medium; .50 – large (Cohen, 1992).

Bonferroni corrections were not used to protect against type II errors, given the small sample size. Therefore, an alpha level of 0.05 (two-tailed) was used throughout.

Relationships between behavioural situational factors and adherence

Substance use difference between adherent and non-adherent episodes were not analysed due to the very small cell frequencies (Field, 2014).

"Was there someone to remind you?"

As shown in Table 8, one person reported having someone to remind them to take their medication at the time of adherent episode and not at the time of non-adherent episode, three people reported there was someone around to remind them at the time of the non-adherent episode but not at the time of the adherent episode. There was no significant difference between these divergent pair of findings (χ^2 =1, p=0.625, φ=0.189).

Table 8: ***Contingency table for "Was there someone to remind you?"***

		Adherent episode		
		No one to remind you	**Someone to remind you**	**Total**
Non-Adherent episode	**No one to remind you**	16	1	17
	Someone to remind you	3	8	11
	Total	19	9	28

"Who were you with?"

As shown in Table 9, three people reported being with someone else at the time of the adherent episode and alone at the time of non-adherent episode; seven people reported the opposite pattern of being alone at the time of adherent episode and with someone at the time of non-adherence. The difference between these was not significant, representing a small to medium effect size (χ^2=1.6, p=0.344, φ = 0.239).

Table 9: ***Contingency table for "Who were you with?"***

		Adherent episode		
		Alone	**With someone**	**Total**
Non-Adherent episode	**Alone**	5	3	8
	With someone	7	13	20
	Total	12	16	28

"What day was it?"

As shown in Table 10, eleven people reported their adherent episode occurring between Monday to Thursday and their non-adherent event occurring between Friday and Sunday. No participant reported the opposite pattern of the non-adherent event occurring Monday to Thursday and the adherent episode on Friday to Sunday. The difference in this pattern was significant with a large effect size, demonstrating participants were more likely to adhere Monday to Thursday and not Friday to Sunday, compared to the reverse pattern (χ^2=11, p=.001; φ=0.650)

Table 10*: Contingency table for "What day was it?"*

		Adherent episode		
		Mon-Thur	**Fri-Sun**	**Total**
Non-Adherent episode	**Mon-Thur**	10	0	10
	Fri-Sun	11	5	16
	Total	21	5	26

"Where were you?"

As shown in Table 11, McNemar's test also demonstrated a difference in being at home or elsewhere between episodes. Adherent episode at home and non-adherent episode elsewhere was more common than non-adherent episodes occurring at home and adherent episodes happening elsewhere (χ^2=9.308 p=.003, φ=0.577).

Table 11: *Contingency table for "Where were you?"*

		Adherent episode		
		Home	**Elsewhere**	**Total**
Non-Adherent episode	**Home**	13	1	14
	Elsewhere	12	2	14
	Total	25	3	28

Daily routine

As shown in Table 12, there was also a significant difference in daily routine between episodes. Participants were more likely to be non-adherent on a day when the routine was different to normal and adherent when their routine was the same as normal compared to the reverse pattern (χ^2=9, p=.004, φ=0.588).

Table 12*: Contingency table for daily routine*

		Adherent episode		
		Same as normal	**Different from normal**	**Total**
Non-Adherent episode	**Same as normal**	9	2	11
	Different from normal	14	1	15
	Total	23	3	26

"I felt ill"

Bivariate comparisons between episode on the measures of somatic experience were carried out using paired t-tests. Cohen's *d* was calculated as a measure of effect size using an online effect size calculator (www.psychometrica.de/effect_size.html#dep) based on the formulae in Borenstein (p. 228, 2009). Conventions for Cohen's *d* are as follows: .20 – small effect; .50 – medium effect; .80 – large effect) (Cohen, 1992)

There was no significant difference in reports of "I felt ill" between episodes ($t(23)=0.31$, $p=0.756$, $d=0.06$).

Forgetting

It was not a key aim of this study to make any between-participants comparisons. However, given the variation in responses to "I completely forgot" on non-adherent episodes, it was of interest to explore potential differences on the primary variables

between those participants who endorsed forgetting as related to their non-adherence and those who did not. The sample was split between participants who strongly agreed or agreed with this statement and those who did not (n1=12, n2=15). This was a basic categorisation of those who may have indicated their non-adherence was unintentional and those where non-adherence may have been intentional to some degree. This exploratory analysis revealed no significant differences on the IMB or affective variables on non-adherent episodes between groups on two-tailed independent t-tests.

Theory-driven Bivariate Analysis

To investigate the main research questions, bivariate analysis consisting of paired t-test comparisons on subscale scores of information, motivation and behavioural skills between episodes was carried out. Differences between positive and negative affect scores were also tested.

It was not possible to analyse the substance use data due to very small cell frequencies for this variable; that is the majority of the sample reported no substance use, therefore there was insufficient variance to test.

Information

Analysis of the information subscale was carried out using both the transformed variable and a bootstrapped paired t-test on the original variable. There were no significant differences between adherent and non-adherent episode on the

information subscale (transformed variable (t(25)=.684, p=0.50, *d*=0.2) and bootstrapped paired t-test (t=-1.113, p=.276, *d*=0.055)).

Personal Motivation

There were no significant differences on scores of personal motivation between adherent or non-adherent episodes (t(26)=.286, p=0.78, *d*=0.041).

Social Motivation

One item pertaining to social norms was analysed separately to the preceding personal motivation items. There was a trend towards higher perceived social support for taking medication at the time of adherent episode compared to non-adherent episode, although this was not significant (t(27)=1.918, p=0.066; *d*=.377). The effect size statistic indicates a small to medium effect size in standard convention (Cohen, 1992).

Behavioural Skills

The difference in behavioural skills between episodes was highly significant, with participants rating their abilities in taking medication much lower in the non-adherent episode compared to the adherent episode (t(25)=-4.949, p<0.001; *d*=0.913). The effect size for this analysis was found to exceed Cohen's (1992) convention for a large effect (*d*=.80)

Affect

There was a significant difference in positive affect (as measured by the PANAS-C 5 item positive affect scale) between episodes: young people rated their positive

emotions more highly at the time of taking their medication than when they missed their medication (t(26)=-3.029, p=0.005 *d*=0.614).

The difference in negative affect between adherent and non-adherent episode was not significant, with a small-medium effect size (t(25)=1.798, p=0.084 *d*=0.363).

There were some significant differences between additional individual affect items suggested by the focus group and critique of PANAS (Peterson et al., 2013). Of the additional negative affect items, feeling weak (*t(*26)=0.848, *p*=0.404, *d*=0.118), out of control (t(26)=1.669, *p*=0.107, *d*=0.291) and helpless (t=1.671, *p*=0.130, *d*=0.266) were not rated differently across adherent and non-adherent episode in the present study. However, ratings of feeling blamed (t(26)=3.148, p=0.004 *d*=0.727) were significantly higher at the time of the non-adherent episode than the adherent episode and show a medium to large effect. All of the additional positive affect items: feeling calm (t(26)=-2.622, p=0.014 *d*=0.632); at ease (t(26)=-2.267, p=0.032 *d*=0.491); content (t(26)=-2.307, p=0.029 *d*=0.475); and satisfied (t(26)=-2.394, p=0.024 *d*=0.510) were rated significantly higher when participants reported adhering to their medication compared to missing their dose.

Associations between IMB variables

The relationships between the IMB primary independent variables were analysed using Pearson's correlation to investigate whether relationships between the constructs were consistent with predictions from the IMB model. The correlation coefficients per episode are presented in the two tables below. Bootstrapped

correlations were used when the relationships investigated included the non-normally distributed non-adherent episode Information variable (Field, 2014).

Table 13*: Pearson's correlations (r) between IMB variables for adherent episode*

	Information	**Personal Motivation**	**Social Motivation**	**Behavioural Skills**
Information		.218 p=.295	-.350 p=.080	.148 p=.471
Personal Motivation	.218 p=.295		.151 p=.443	.537 p=.006*
Social Motivation	-.350 p=.080	.151 p=.443		-.124 p=.546
Behavioural skills	.148 p=.471	.537 p=.006*	-.124 p=.546	

**statistically significant p<.05*

Table 14*: Pearson's correlations (r) between IMB variables for non-adherent episode*

	Information	Personal Motivation	Social Motivation	Behavioural Skills
Information		-.134 p=.522	-.352, p=.066	.483, p=.015*
Personal Motivation	-.134 p=.522		.331 p=.086	-.486 p=.010*
Social Motivation	-.352, p=.066	.331 p=.086		r=-.801, p<0.001*
Behavioural skills	=.483 p=.015*	-.486 p=.010*	-.801 p<0.001*	

**statistically significant p<.05*

There was a significant association between personal motivation and behavioural skills, which was consistent across both episodes (adherent episode r=-.537, p=.006; non-adherent episode r=-.486, p=.010).

Theory-Driven Exploratory Multivariate Analysis

To explore the relationship between the IMB variables and adherence beyond the bivariate associations, multivariate analysis was conducted. The effect size of the relationship between behavioural skills and adherence was very large. Multivariate analysis would enable investigation of the combined and independent contribution

of behavioural skills and the other significant predictors (positive affect, routine, day and location) of non-adherent episodes.

The outcome variable was dichotomous (adherent or non-adherent episode), therefore a logistic regression model was used. Conditional logistic regression is the appropriate model for repeated measures or matched-pairs data, as in this case, to avoid violating the assumption of independence in logistic regression (Tabachnik & Fidel, 2006).

Logistic regression models are based on binomial distributions where the independent variables predict the log odds of binary group membership (the adherent or non-adherent event) rather than the proportion of variance in the dependent variable. Conditional logistic regression is a fixed effects model, with matched data points from the same participant, compared to the random effects model in standard logistic regression. This minimises the degrees of freedom and maximises the statistical power of the model (Chatterjee & Hadi, 2006). However, one should adopt a cautious approach to conditional logistic regression in small samples and be aware of possible violations to its assumptions (Greenland, Schwartzbaum, & Finkle, 2000). Influential and outlier variables, as well as multicollinearity, were tested as the assumptions of conditional logistic regression.

Multicollinearity

Multicollinearity refers to the degree to which two or more independent variables are related in a linear way, or could be predicted from one another with significant

accuracy. Severe multicollinearity causes invalid results about individual predictors in a regression model, without necessarily impacting on the model as a whole (Chatterjee & Hadi, 2006). To test the multicollinearity between predictor variables, the variation inflation factor (VIF) and tolerance should be calculated. The extent to which the regression model can withstand multicollinearity is measured by tolerance; a value close to 0 indicates a problem. The VIF indicates how much the multicollinearity is inflating the estimates of standard error; a value greater than 5 indicates the independent variables are very closely related (O'brien, 2007). If no relationship exists between any of the predictor variables, the VIF and tolerance will equal 1 (Chatterjee & Hadi, 2006).

Outliers and influential observations are quantified using leverage metrics (Field, 2014). In regression models, an observation with a large difference between the predicted and observed value (which can be measured by statistics such as Pearson's standard residual) is defined as an outlier. Such variables may indicate a data error or reflect an unusual case and may have undue influence on the analysis. The leverage value (such as DfBeta) measures how far the observation deviates from the mean (Field, 2014). A critical value greater than 3 for Pearson's standard residual and greater than 1 for DfBeta indicate problematic observations (Chatterjee & Hadi, 2006).

Given the small sample size, it was likely that individual cases could have a large influence on the regression models. 'Overfitting' occurs when the number of

parameters is too great relative to the number of observations, therefore was also a particular issue with the current sample (Babyak, 2009). A danger with overfitting is for the model to be explaining random error, rather than the data itself, due to too few observations. Conditional logistic regression can exhibit considerable bias in the absence of a large sample when there are too many covariates for the data to support (Greenland, Schwartzbaum, & Finkle, 2000). Furthermore, with categorical data there is a risk of large standard error caused by small cell sizes.

Field (2014) advises at least ten observations per independent variable for logistic regression analysis. Because of the small sample size and dangers of overfitting (Babyak, 2009; Greenland, Schwartzbaum, & Finkle, 2000), it was necessary to restrict the multivariate analysis to two predictor variables (and these models should still be interpreted with caution).

Because non-significant results had been obtained for information and motivation in the bivariate analysis, behavioural skill was selected as the main theoretical variable of interest in the regression modelling.

Multivariate analysis was conducted to explore the key relationship between behavioural skills and adherence. The IMB model predicts that mental health moderates the central IMB variables (information, motivation and behavioural skills). As there was a bivariate relationship between positive affect (conceptually related to mental health) and adherence, positive affect was added to behavioural skills as

independent variables in a conditional logistic regression model. . The positive affect 5-item scale was included and not the individual additional items suggested by Peterson and colleagues (2013) to reduce the chance of type II error by using a scale with greater variance and reliability.

Correlations between behavioural skills and positive affect were investigated as an initial test for potential mulitcollinearity problems. To be problematic in conditional logistic regression, correlation coefficients would need to be greater than 0.70 (Chatterjee & Hadi, 2006). For non-adherent episode behavioural skills and positive affect were significantly correlated (r=.502, p=.011). There was no correlation between behavioural skills and positive affect for adherent episode (r=.070, p=.734). These statistics suggested there may not be a multicollinearity issue with these variables.

Conditional logistic regression was run as Cox regression in SPSS as there is no available option to run conditional logistic regression in this software. Cox and conditional logistic regression (CLR) are algebraically equivalent (Greenland, Schwartzbaum, & Finkle, 2000).

CLR model including behavioural skills and positive affect

The CLR assumptions were tested for this model (Table 15): VIF and tolerance values were both close to 1; Pearson's standard residuals demonstrated no values higher than 3; DfBeta measure of leverage were not above 1, therefore no assumptions were violated.

Table 15*: CLR Model with Behavioural Skills and Positive Affect*

	B	Std. Err.	Sig.	Exp(B)	95% Confidence Interval	
Behavioural Skills	-.434	.236	.066	.648	.408	1.029
Positive affect	-.181	.122	.138	.834	.657	1.060

An overall model including both behavioural skills and positive affect was significantly predictive of adherent episode ($\chi^2(2)=14.634$, p=0.001). After controlling for shared variance between behavioural skills and positive affect, there were non-significant associations with non-adherent episode for each predictor (behavioural skills AOR=0.65, 95%CI 0.41-1.03, p=0.066; positive affect AOR=0.83, 95%CI 0.66-1.06, p=0.138).

As part of the exploratory multivariate analysis, behavioural skill was tested with other significant bivariate predictors of episode, even though the latter were not included in the IMB model. The results of these CLR models are below.

Behavioural skills and routine

A model including behavioural skills and routine significantly predicted episode outcome ($\chi^2(2)=14.271$, p=0.001). However, the bivariate effects of both these variables were eliminated when controlling for shared variance (routine AOR=0.14,

95%CI 0.01-2.70, p=0.195) although there is a weak association with non-adherence for behavioural skills (AOR=0.64, 95%CI 0.39-1.06).

Table 16*: CLR Model: Behavioural Skills and Routine*

	B	Std. Err.	Sig.	Exp(B)	95% Confidence Interval	
Behavioural Skills	-.446	.255	.080	.640	.388	1.055
Routine	-1.942	1.499	.195	.143	.008	2.704

The large confidence intervals for routine indicate a problem with this model. Upon investigating the CLR assumptions, although multicollinearity and outliers were within acceptable limits, one DfBeta value was problematic. From inspection of the data, one person was both adherent and non-adherent when their normal routine was not followed and this pattern appears to have significantly influenced the model. This may be expected in CLR models with small sample sizes, as mentioned above. In this model, two of the four cells have cell frequencies less than 5, which is highly problematic for this statistical test (as mentioned earlier in this chapter) (Greenland, 2000). Therefore, this model should be interpreted with caution.

Behavioural skills and day

It was not possible to fit a CLR model with behavioural skills and day, evidenced by very large standard errors. Investigation of DFBeta diagnostics and Pearsons'

standard residuals demonstrated there both were outliers (on three cases) and influential cases (on three cases) within the dataset. In addition, one of the cells (for non-adherent episode on weekday and adherent episode on weekend) contained 0 responses. All of these factors prevented the interpretation of a regression model with behavioural skills and these two variables.

Behavioural skills and location

It was not possible to fit a CLR model with behavioural skills and location, evidenced by very large standard errors. The diagnostics were not interpretable due to exceptionally large variation in the values. It is likely this is due to the small sample size limiting the cell frequencies for the location variable.

Prospective data

Six people completed at least one prospective questionnaire. Frequencies of categorical data are not reported here due to the small numbers. Descriptive data of the IMB, affective and somatic variables are presented in Table 17 below.

Table 17*: Descriptive statistics for prospective data*

Variable (minimum – maximum score)	**Non adherent episode *(n=6)***	**Adherent episode *(n=4)***
	Mean (SD)	**Mean (SD)**
Information (4-20)	19 (1.54)	19 (1.55)
Personal Motivation (8-40)	17.5 (4.04)	20.17 (7.83)
Social Motivation (1-5)	3.75 (1.89)	4.33 (0.82)
Behavioural Skills (8-40)	37.25 (11.59)	36.17 (9.70)
Positive affect PANAS-C 5 item (5-25)	6.00 (2.00)	13.83 (4.67)
Negative affect PANAS-C 5 item (5-25)	8.75 (3.30)	7.67 (2.66)
I felt ill (1-5)	3.75 (1.89)	4.00 (1.55)
Choice (1-5)		2.33 (1.21)
Forgot (1-5)	1.25 (0.50)	

Unfortunately, the sample size was too small to carry out any inferential statistics on this data.

Summary of Findings

In summary, bivariate analyses of differences within individuals between adherent and non-adherent episodes demonstrated the central IMB construct of behavioural skills, as well as positive affect, were significantly higher at the time of adherent compared to non-adherent events. The following individual affect items were significantly higher at the time of the adherent episode than the non-adherent episode: calm, at ease, content, satisfied. Ratings of blamed were significantly lower at the time of the adherent event. The situational behavioural variables that differed between episodes were: day of the week (week day or weekend), being home or elsewhere and daily routine being the same as normal or different to normal. Non-adherent episodes were more likely at the weekend, outside of the home and when routine was different to usual. There were no statistically significant differences between adherent and non-adherent episodes on negative affect or social motivation, although both of these comparisons demonstrated small-medium effect sizes.

Multivariate analyses (conditional logistic regression) demonstrated that behavioural skills and positive affect together significantly predicted non-adherent episodes. There were statistically non-significant effects of each predictor when controlling for the other, although the adjusted odds ratio for behavioural skills probably represents a small to medium effect that did not reach significance due to low

power. Conclusions could not be drawn from the conditional logistic regression models including behavioural skills and routine, day or location due to the small sample size leading to violations of the CLR assumptions or creating problems in interpreting the CLR models.

Discussion

The aim of this research was to investigate situational psychological and behavioural correlates of episodic medication adherence amongst young people with PHIV+. The IMB model informed the main psychological constructs under investigation, which included adherence-related behavioural skills, personal and social motivation, information, and mood, as measured by positive and negative affect.

Overview of study findings

Behavioural skills

A person's objective and perceived abilities to adhere to their medications are referred to as behavioural skills in the IMB model. This includes having both confidence and skill to self-cue and self-administer ART, incorporate these into the daily routine, manage possible unwanted effects and reinforce oneself to continue to adhere over time (Fisher, Fisher, & Shuper, 2014). The significant effect of behavioural skills on adherence was particularly strong in the present study, exceeding Cohen's (1992) convention for a large effect. This is in keeping with the theoretical model, which positions behavioural skills as the central construct and most proximal to adherence behaviour. That is, an individual's adherence-related

information and motivation are limited by their ability to enact adherence-related behavioural skills (Fisher et al., 2008).

Behavioural skill was predictive of non-adherence when combined with situational positive affect in a multivariate model. In controlling for shared variance with positive affect, the effect of behavioural skills was no longer statistically significant (p=.066). However, it is likely this finding was due to a lack of adequate power to support the multivariate analysis; the adjusted odds ratio indicates a small sized effect. With a larger sample, therefore, it may have reached statistical significance (discussed further in 'Limitations' section, below). This may suggest that perceived confidence in one's abilities to adhere could be an important determinant of non-adherence regardless of situational levels of positive feelings. Therefore, although this finding was not significant with the current sample, the potential clinical implications of this are tentatively discussed in a later section of this chapter.

In the present study, the behavioural skills subscale targeted the young person's perception of their adherence-related skills. This perceived abilities component has also been labelled 'self-efficacy' in the adherence literature. Bandura's theory of self-efficacy asserts that possession of knowledge or skills is insufficient to impact on behaviour, and that confidence in one's abilities is a crucial determinant of action (Bandura, 1986; Brown, Littlewood, & Vanable, 2013). Self-efficacy is not a stable trait (Strecher, et al, 1986). The level of confidence in the capacity to enact a behaviour is likely to vary over time and across situations, impacting on one's

performance of the behaviour. Self-efficacy has been studied extensively across a variety of health behaviours in adults and adolescents, including smoking behaviours (Gwaltney, Shiffman, Balabanis, & Paty, 2005; Van Zundert, Engels, & Kuntsche, 2011), consumption of dietary fat and sugar (McClain, Chappuis, Nguyen-Rodriguez, Yaroch, & Spruijt-Metz, 2009; Pawlak & Colby, 2009) and condom use (Chirinda & Peltzer, 2014; Walsh et al., 2011) and demonstrated to vary according to situation.

Self-efficacy has also consistently been associated with adherence between individuals in a variety of populations and health conditions (e.g. Bucks et al., 2009; Griva, Myers, & Newman, 2000). Relationships between higher levels of self-efficacy and higher ART adherence have been demonstrated between-participants in the PHIV+ population in Thailand (Kang, Delzell, Chhabra, & Oberdorfer, 2014) and the USA (Rudy, Murphy, Harris, Muenz, & Ellen, 2010). The findings of the current study support the theoretical understanding of self-efficacy as a dynamic construct that changes situationally. Causality cannot be inferred from the current study, that is low levels of behavioural skills cannot be said to cause non-adherence to ART, because the design of this study was not experimental. However, there appears to be a clear variation in self-efficacy within individuals, which seems to be related to inconsistent ART adherence.

There are a number of possible theoretical explanations for the variation in self-efficacy observed between adherent and non-adherent episodes. Bandura suggested that higher confidence is followed by greater effort and persistence in

solving a problem, even when faced with a challenge (Bandura, 1986). There may have been different challenges faced by the young participants between adherent and non-adherent episodes in the present study, which subsequently may have impacted on the degree of effort and confidence in adhering to ART.

Other possible explanations for the differences in behavioural skills between episode could be methodological. Despite using a new and unvalidated scale, the reliability was very good across the behavioural skills subscales. Measurement error would reduce the size of effect found, yet the results indicate a large effect of behavioural skills on adherence. Finally, expected correlations with motivation were found (discussed under 'Personal Motivation' below).

It is possible that there was recall bias in the participants' responses, leading to significant differences between episodes. However, there were no differences in the motivation or information scales between episodes, therefore it is unlikely: recall bias would be more likely to have consistently affected the findings across all subscales, which was not the case.

The difference in behavioural skills between episode could also be due to post-hoc rationalising on the part of the participants. A young person may have decided they must not have felt confident at the time of non-adherence by virtue of having not taken their medication at that same time.

Social motivation

There were no statistically significant differences found between episodes on social motivation. However, there was a small-medium sized effect towards higher perceived social pressure at the time of adherent episodes than non-adherent episodes. This trend may have reached statistical significance with a greater number of participants and it is possible that these findings were subject to a type II error. The social motivation subscale could be expanded to include more items, to enable this construct to be measured in a more robust way. This construct was measured with a single item, taken from the LifeWindows IMB Adherence Questionnaire, from which limited conclusions can be drawn (The LifeWindows Project Team, 2006). However, this was the primary social motivation from the LW-IMB-AAQ; two additional social motivation items referred to the perception of support from clinic staff. This was unlikely to vary my situation, thus was excluded from the scale in this stud. By increasing the number of scale items, the subscale reliability might increase.

Kalichman, and colleagues, criticise the IMB model because of the inconsistent association between motivation and adherence behaviour (Kalichman, Picciano, & Roffman, 2008). Construct validity may be problematic in some measurements of social motivation; objective social support and perception of social support (one aspect of social motivation) may be conflated (e.g. Rongkavilit, et al, 2010). In the current study, the single social motivation item asked participants to what extent they thought important people were supportive of their ART regimen. This item

seems to clearly ask about perception, not about the presence or absence of social support.

Personal motivation

There were no significant differences between adherent and non-adherent episodes on the personal motivation subscale. It is unlikely the current findings were due to measurement error or sample size due to the very small size of effect. There were, however, significant relationships between personal motivation and behavioural skills on both adherent and non-adherent episodes. This relationship is in keeping with the IMB model: the main effect of motivation on adherence is mediated through behavioural skills, although it was not possible to test a mediating relationship due to the lack of power for multivariate analysis.

It is possible that some aspects of adherence motivation do change over time or according to situation, but in the aspects measured in the present study were stable. The relationship between personal motivation (or outcome expectancies – one of its components) and adherence is inconsistent in the literature and does not always differentiate good adherers from bad adherers in between-participant studies (Brown et al., 2013). In the current study, personal motivation to adhere does not appear to differentiate adherence within individuals. This is consistent with the findings of an investigation in adults with Thalassaemia that used a similar methodology to the present study (Vosper, Evangeli, Porter, & Shah, 2013). Although there were significant effects of self-efficacy *and* outcome expectancy in a

multivariate model, there was no independent effect of outcome expectancy on episodic adherence.

The IMB model also suggests some influence of personal motivation (albeit to a lesser degree) on adherence behaviour itself, which was not found in the present study. There may be alternative theoretical explanations for this, drawing on principles from other health-behaviour theory. A critique of continuum models, such as IMB, is the absence of "post-intention" explanations (Sheeran, Webb, & Gollwitzer, 2005). That is, once motivation is established, there is little account of how these are actually translated into behaviour: there may be further barriers to adhere despite good motivation to do so and high confidence in one's abilities to do so. One theory, the Health Action Process Approach (HAPA) (Schwarzer, 1992; Schwarzer & Luszczynska, 2008), describes postintentional volitional processes that enable an intended behaviour to be enacted, such as action planning and implementation intentions (discussed further below, in relation to 'forgetting') (Brandstätter, Lengfelder, & Gollwitzer, 2001; Sheeran et al., 2005). In the present research, in relation to the lack of significant difference in personal motivation between adherent and non-adherent episode, there may have been a difference in post-motivational processes that would account for the difference in adherence behaviour.

Information

There were no significant differences within-participants on the measure of information. Scores on this scale were very high for all participants on both episodes, therefore it is possible the lack of difference is due to a ceiling effect. It is also possible that information remains static and does not vary by situation despite attempts by the author to phrase the questionnaire items situationally.

In the IMB model, information (about regimen, the importance of high levels of adherence, potential drug interactions and possible side effects) is described as an essential prerequisite for adequate adherence (Fisher et al., 2014). The influence of information is mostly mediated through behavioural skills except for simple and automated behaviours, which might be driven directly by information (Fisher et al., 2008). However, given ART adherence is neither simple nor automated due to the complexity of most regimens, it may not be the case that information has a direct, influence on adherence. Previous studies using the IMB model have found a lack of direct relationship between information and ART adherence (Starace, Massa, Amico & Fisher, 2006; Horvath, et al, 2014). In previous studies with HIV+ adolescents, ART-related knowledge has seldom been found to be a barrier to actual adherence behaviour. In Murphy and colleagues' (2003) study of the association between non-adherence and possible predictors, less than 6% of 114 young people endorsed an information-related item ("confused about what to take") as a reason for not taking ART. Self-assessed HIV knowledge was not related to adherence in a study of HIV+

adults in the USA (Nelsen et al., 2013). It may be that ART-related information and knowledge is necessary but not sufficient for adherence to occur.

The information subscale had high internal consistency, contrary to the LifeWindows validation study. In the original measure, there were nine information subscale items with low internal consistency, explained by the diverse aspects of an ART regimen of which one would need knowledge, therefore items were not expected to inter-relate (The LifeWindows Project Team, 2006). Less variation may have occurred in this study, where all items were related to a very specific knowledge base, relating to those aspects of the information construct that could plausibly change according situation.

Affect

Within-participant differences in negative emotions were not significantly associated with adherent or non-adherent episodes as measured on the standard five-item PANAS-C scale, although, there was a small-medium sized effect towards greater reported negative affect at times of non-adherence. Previous studies have found variable relationships between negative affect and adherence behaviour (Gonzalez et al., 2007). In the current study, however, there may have been insufficient power to support the analysis of the negative affect scale and additional items, the size of effect indicates a larger sample may have yielded significant results.

The additional negative affect items suggested by the pilot group were generally non-significant between episodes. However, feeling blamed was significantly higher at the time of a non-adherent event with a medium-large effect. This could have been due to the non-adherent event itself, rather than a causal influence of feeling 'blamed' on the non-adherent event. That is, young people may have felt blamed because they did not take their ART, rather than not taking their ART because they felt blamed. This association could be explored further using Ecological Momentary Assessment methods (Shiffman, Stone, & Hufford, 2008), which would enable closer study of the temporal associations between the feeling and the non-adherent event. Such methods have been employed to investigate momentary changes in affect related to stages of smoking cessation in adolescents (Hoeppner, Kahler, & Gwaltney, 2014). By recording scale ratings of young participants' affect at fixed time intervals, the authors were able to conclude that there were momentary changes in affect related to momentary self efficacy immediately before and after a quit attempt. A similar technique would enable fluctuations in 'blamed' feelings (or other feelings) to be measured and analysed according to the proximity to the non-adherent episode.

Situational pleasant emotions were associated with episodic medication adherence, with higher ratings of positive affect on the standardised five-item scale at the time of an adherent episode compared to a non-adherent episode. As well as this, all additional positive affect items (added to measure non-activated positive affect)

were significantly higher during ART adherent episodes than non-adherent episodes. This highlights the utility of scale measurement for psychological states.

An alternative approach to measurement of affect would be to draw on the circumplex model of core affect (Yik, Russell, & Steiger, 2011). In this framework, affect is divided according to dimensions of valence and activation, resulting in four quadrants of emotion: pleasant/activated, unpleasant/activated, pleasant/non-activated, unpleasant/non-activated. In the current study, it appears that both activated and non-activated positive affect varies according to adherent or non-adherent episode. However, there is no comparable measure of negative affect. Future research could investigate differences in situational affect along these four dimensions.

This finding correlates with the wider ART adherence literature implicating mental health difficulties as a barrier to adherence (Kapetanovic et al., 2011; Mellins & Malee, 2013). Previous research investigating mental health has tended to focus on diagnosis as an index of psychopathology. The presence or absence of a current or historic psychiatric diagnosis may be inadequate in measuring symptoms of psychological distress. The absence of a diagnostic label does not necessarily equate to an absence of psychological distress. Alternatively, a diagnosis may suggest that a person has received psychological support or treatment, which might reduce the impact of mental health symptoms on adherence. Further, in assigning people to groups of diagnoses or presence or absence of mental disorder, there is loss of

variability in the data collected. That is, the extent to which individuals experience particular symptoms or psychological states is not recorded in as comprehensive a way that would be more possible with scale measurement. Therefore, particularly in event-level designs, it may be appropriate to use scales to measure affective states (as in the current study).

Forgetting

Young people were not asked about intentional non-adherence. However, more than a third of the sample in the present study did not agree that their non-adherent event was due to forgetting. This is an often-cited explanation for failing to take medication in the between-subjects adherence literature with this population (MacDonell, Naar-King, Huszti, & Belzer, 2013). It may be reasonable to cautiously assume an element of intentional non-adherence with this subset of participants. Participants may have deliberately chosen not to take their medication for particular reasons in a particular situation. The significant episodic variables in this study may have differential relationships depending on whether the non-adherence was intentional or unintentional. In comparisons between the subset of participants who agreed with forgetting as a reason for non-adherence and those who did not agree, there were no significant differences on any of the primary variables (IMB or affect). However, due to the small number of participants in each group, there is an increased risk of Type II error. The study was not powered for any between-groups comparisons, which require larger samples, therefore these analyses may have lacked sufficient power to detect significant effects. Further, the way in which participants were grouped may not have been valid. Participants who 'strongly

disagreed' and 'neither agreed or disagreed' with forgetting as a barrier to their non-adherent episode may not have been a homogenous group. In further studies with larger samples, analysis of variance tests would allow for investigation of potential differences between participants depending on to what extent they endorsed forgetting as an explanation (without having to condense participant responses into groups, thereby reducing the statistical power). A larger dataset would have enabled further investigation of whether the relationships between other variables of interest might be different according to intention to adhere or not.

Forgetting may be a particularly pertinent factor, given what is known about potential cognitive difficulties experienced by PHIV+ young people (Puthanakit et al., 2010). Deficits in working memory may help to explain episodic non-adherence. Particularly in the case of changes to usual routine and location, an absence of relied-upon structural cues would necessitate a greater reliance on working memory, which may be impaired to some degree in the PHIV+ population, as discussed in the introduction (Laughton, Cornell, & Boivin, 2013; Smith & Wilkins, 2014). There was no measure of cognitive function or working memory ability in the current study. In future research, a baseline index of cognition would enable investigation of differences in forgetting as related to overall cognitive or memory ability.

The present results suggest that it may be valuable to move beyond viewing 'forgetting' as a reason for non-adherence and towards a focus on which situations are more or less likely to be associated with forgetting. Perhaps the use of specific

strategies in particular situations is especially adaptive, such as the common method of writing down reminders. In other situations there may be obstacles to using usual reminders, which could interfere with the adherence process. This highlights an important clinical implication (discussed further in a later section): a greater understanding of situational factors implicated in non-adherence would help clinicians and young people to plan in advance strategies to manage such situations.

Behavioural situational variables

There were significant differences between episode in routine, location at the time of medication and day of the week. Participants' adherent episodes were more likely to occur at home and non-adherent episodes elsewhere, than the opposite pattern. Participants were more likely to be adherent on a weekday (Monday to Thursday) and non-adherent at the weekend (Friday to Sunday) than the reverse. Participants were more likely to be non-adherent if their routine was different to usual and adherent when their daily routine was normal. Being away from home and having a change in routine are often-cited reasons for non-adherence in between-participant studies (Buchanan et al., 2012; Murphy et al., 2003; Rudy, Murphy, Harris, Muenz, & Ellen, 2009). The findings of the present study are in keeping with this literature, and with the within-participants differences found in Vosper, et al, (2013) in explaining the variation within individuals rather than between individuals.

The differences between episodes on behavioural variables suggest it may have been more difficult to adhere in particular contexts. If a young person's daily routine was

disrupted, it might follow that their medication routine was similarly disrupted. Having a medication routine is associated with greater adherence in global adherence studies (Genberg, Lee, Rogers, & Wilson, 2014). It is possible that different daily activity interferes with the planning and cueing of an adherent event. Similarly, the weekend may be linked to an increase in social activities, which in turn might lead to a forgotten dose.

It is possible that the psychological variables found to vary between episode (behavioural skills and positive affect, in particular) may mediate the relationship between behavioural situation and adherence. This would suggest, for example, that young people might feel more confident in particular contexts, which would then affect their adherence. Unfortunately, this could not be adequately tested in the current study due to the small sample and insufficient power for multivariate analysis.

Additional factors

Unwanted adverse effects are considerable barriers to global adherence amongst the PHIV+ population, as investigated in between-subjects research (e.g. Macdonell, Naar-King, Murphy, Parsons, & Huszti, 2011). Participants' actual experience of such effects was not investigated in the current study. Rather, the focus was on the anticipation of and perceived abilities in managing possible side effects at the time the ART dose was due (as the medication would not yet have been, so would not have caused any unwanted effect). This anticipation was measured as part of the personal motivation subscale and subjective confidence in managing side effect was

measured as part of the behavioural skills subscale (item: “I was confident I could manage any side effects”).

The complexity of the medication regimen was not included in the episodic questionnaire, as this was unlikely to change situationally over the course of the four-week study period. This information was extracted from the AALPHI baseline data. With the exception of one young person who was taking a twice-daily regimen, all participants in the current sample reported once-daily ART regimens. There is a suggestion in the literature that increased treatment burden and complexity is likely to be associated with global non-adherence and lower pill burden is related to increased overall adherence (Nachega et al., 2014). However, the findings from this study suggest that other contextual factors (such as those already described above) must contribute to episodic non-adherence in this group, beyond the impact of treatment burden, as the treatment regimen was mostly the same for each person.

The difference in alcohol and substance use between adherent and non-adherent episodes was not analysed here due to such small numbers of participants who reported using either alcohol or other substances. Participants may have deliberately chosen to report on particular adherent and non-adherent episodes when they were not using alcohol or illicit substances, due to concerns about researcher judgement. Alternatively, this could be related to low baseline levels of reported alcohol use (18 people answered “never”, in response to how often do you drink alcohol at enrolment to AALPHI), in which case there would be little to no

expected variation between episodes. Overall rates of alcohol use in this sample were consistent with the AALPHI population and lower than HIV-exposed but not infected controls.

It could be inferred from the current findings that alcohol use may be less important in episodic adherence within-individuals compared to the findings in global adherence studies (e.g. Hosek, Harper, & Domanico, 2005). Kiene and Subramanian investigated the association of alcohol use and unprotected sex using an event level design (Kiene & Subramanian, 2013). The authors cited between-group, global studies of alcohol and condom use, which describe increase in unprotected sex with increased use of alcohol (Kalichman, Simbayi, Jooste, & Cain, 2007). At the event level, however, these associations are not found; in some situations, the opposite effect occurs. This highlights the utility of event-level designs for inferring relationships in particular contexts. Although it was not possible to carry out inferential analysis of difference on the alcohol use data in the current study, the levels of use were descriptively low across both episodes. Further analysis on a larger dataset would be required to fully describe the relationship between episodic adherence and alcohol use. The findings of the current study may, however, indicate a possible differential relationship between use of alcohol and adherence at the event level compared to findings at the global level. It would be of interest to focus on this association in future research.

There were very low rates of onward disclosure in the current sample, with 38% of the sample having not disclosed their status to any other person outside of their family and 72% having disclosed to two other people or fewer. In qualitative reports, there has been suggestion of PHIV+ young people deliberately not taking prescribed ART in an effort to maintain a level of secrecy around their diagnosis (Denison et al., 2015). An association between onward disclosure and less hiding of medication and higher CD4+ counts has also been found in PHIV+ (Calabrese et al., 2012). There was no significant between episode relationship between adherence and whom the young person was with in this study, although there was a small to medium effect size. Due to the small sample size, responses were grouped into 'alone' versus 'not alone'. Moreover, it was not possible to investigate differences between exactly who was around at the time of the ART dose. There may be differences in situational adherence depending on whether the accompanying person was aware or not aware of the PHIV+ participant's status. This was not part of the current questionnaire, but would be of interest to measure in future studies.

In the baseline AALPHI data from the current participants, 41% of young people rated their adherence as 'excellent'. Given the criterion of at least one missed dose over the previous two months, the present sample could also be categorised as 'inconsistent adherers'. This may not necessarily fit with a subjective rating of 'excellent' adherence: these young people may have overestimated their level of adherence at AALPHI baseline. Alternatively, the perception of what 'excellent' adherence means for the individuals in this sample may have allowed for occasional

missed doses. The present study suggests that there are contextual factors related to adherence that vary according to situation, which may be applicable to PHIV+ young people categorised even as 'excellent' adherers.

Limitations

No validated situational measures were available to measure adherence in this population (or any others). The reliability and validity of the measures and scales should be approached with caution. However, the scales to measure the IMB constructs developed for this study were adapted from an existing tool (LifeWindows) in consultation with a lead author of this measure and of the theories from which it was derived (Amico, personal communication; Amico, 2011; Fisher, Fisher, Amico, & Harman, 2006). In addition, a piloting phase took place to explore the meaningfulness, applicability and comprehensiveness of the items to a focus group of young people. These young people also commented on the wording of the scales to ensure, relevance, clarity and appropriateness for a situational context. During this phase, the wording of a number of items was amended and some items added. There was a free text section of the questionnaire for additional comments about salient factors in relation to the adherent or non-adherent day from which no extra themes arose. Therefore, although the measures were not validated, steps were taken to ensure the questionnaire used was well constructed. For example, item-total correlations and whether dropping items resulted in increased reliability were examined. The motivation subscale was adapted as a result of this process. The good internal reliability of the scales for each episode and the significant effects

identified in spite of a small sample size suggests the measurement of the constructs was acceptable.

It was not the focus of the present study, nor was it possible to establish, a valid, descriptive level of anxiety and depressive symptoms in the current sample. Although all participants completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) as part of their inclusion in the AALPHI study there was a considerable delay between completing this measure and the enrolment to this study. It was possible that young people completed the HADS up to 12 months or greater prior to the present study. Studies of test-retest reliability in adolescents demonstrate adequate reliability over periods of only two weeks (e.g. White, Leach, Sims, & Atkinson, 1999). Indeed, the HADS is a measure designed to assess levels of clinical anxiety or depression symptoms at baseline and to measure change over time. Therefore, it is not possible to assert that the HADS scores would be reliable; there was no accurate characterisation of the level of clinical mood symptoms in the sample and therefore no description of the global state of mood in these young people. There was a single indicator of significant mental health morbidity from the AALPHI baseline data: whether the young person had ever been referred to CAMHS. To the extent that a history of CAMHS referral indicates psychiatric issues, it would be possible to say the current sample were not from a clinical mental health population. However, this is a very crude measure on which to base an assumption of the absence of mental ill health. Therefore, in a further study greater consideration could be given to characterising the mental health of the sample.

There may be differences in psychological contextual factors between adherent and non-adherent episodes in participants with a history of current or previous mental health disorder.

The participants in the current study were a subsample of the AALPHI cohort study. Participants were between age 13 and 22, which is in keeping with previous studies of adolescents; the mean gap between puberty and adulthood (measured by social and financial independence) is twelve years in the UK (Viner, 2012). However, it is possible that different contextual factors may be applicable to 13 year olds and 22 year olds as they may be at different developmental stages. For example, it might be expected for almost all 13 year olds to be attending school and living with a care-giver; at 22, one might be living independently and have a job. With a larger sample, it would be possible to analyse possible differences in adherence-associated contextual factors between age groups and subsequently control for age in multivariate analysis.

There were significant statistical issues in the conditional logistic regression analysis, most likely due to a lack of variability in categorical data caused by too few participants. This was not wholly unexpected; the study was powered for bivariate analysis. A larger sample may have enabled more detailed multivariate analysis of the relationships between the significant episodic variables. With more cases per factor, models are less influenced by leverage and residuals of particular individual outliers. More participants may also have enabled more detailed analysis of the

categorical variables. Categorical data were grouped due to small numbers of cases per cell, although this was still not sufficient to support the conditional logistic regression models for day and location. With a greater number of data, these variables could have been analysed without the necessary grouping.

The small sample may also have compromised generalizability to the wider AALPHI cohort. However, this project recruited from multiple centres and employed a systematic sampling strategy whereby every young person who was eligible at the selected centres was approached and offered the opportunity to participate. The response rate was good (81%) and demographic data indicate similar characteristics to the overall CHIPS cohort and specific AALPHI cohort, therefore issues with generalizability may be minimal.

Asking participants to answer the questions about a particular episode of non-adherence within the last two months possibly served to limit erroneous recall of specific details. However, there was no record of exactly how long ago the non-adherent episode and adherent episode took place. In a similar project, the mean number of days ago for the non-adherent episode was 10 days; for adherent episode, 1.3 days ago (Vosper et al., 2013). It is possibly there was a similar time lapse from episode to questionnaire completion in this study.

Although most participants agreed to take part in the prospective component to the study, attrition rate was high and only four participants completed the questionnaire

prospectively for both adherent and non-adherent episodes; two more participants completed the adherent episode only. It is possible that these two participants did not have a further non-adherent episode in the four weeks following enrolment to the study and therefore could not fully participate in both prospective questionnaires. The SMS reminders were designed to promote the ease of completing the questionnaire, but a number of steps were required in order for this to happen: the prospective questionnaire was only available online. Participants would have required access to the internet at the time of the SMS reminder to complete the questionnaire straight away, although could have completed it at a later point. However, if there was a delay from the SMS reminder to being able to access the questionnaire, this allowed a greater margin for forgetting to complete the questionnaire. SMS reminders were reduced from daily to three-daily as initial participants opted out of the reminders without completing the questionnaire. It may have been better to keep the daily SMS reminders in order to promote the second part of the project. However, high drop out rates for prospective studies are well documented, therefore it could be that more participants recruits were needed initially to account for high attrition (although this could have led to bias). Alternatively, a larger financial reimbursement or more direct prompting may have improved the response rate for the prospective questionnaires.

Strengths

In spite of the weaknesses cited above, there were a number of strengths of this project. The novel design enabled the investigation of situational factors, an alternative and potentially complementary perspective to studies of global.

Temporal variation and the dynamic nature of the variables under investigation enabled a stronger association with the adherence behaviours to be implied, although causation cannot be established.

Using scales to investigate psychological constructs is a more valid method of measurement compared to survey responses. Previous studies (e.g. Macdonell et al., 2011) have required participants to select which of a list of factors were relevant to their adherence or non-adherence using dichotomous, forced choice 'yes' or 'no'. This method overlooks subtle quantitative differences in the degree to which a factor may or may not be relevant. Psychological variables measured with multi-item scales increases validity, reliability and enables grouping of related constructs for analysis by subscale. The categorical measurements in the present study were analysed separately.

This research used elements of the Day Reconstruction Method (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004) to scaffold participants' accurate remembering of the adherent and non-adherent episodes. The behavioural situational questions were presented at the start of the questionnaire to orient participants to the particular time and place of the adherent or non-adherent event and reduce recall bias. Research participants who give self-reported accounts about various psychological factors in any cross-sectional study are required to form some retrospective judgement. For example, many standardised and widely used measures of mood, such as PHQ-9 (Kroenke, Spitzer, & Williams, 2001) and GAD-7

(Spitzer & Kroenke, 2006), require participants to rate their emotional state over the past two weeks. To ask participants to reflect on their feelings and mood at the time of a particular episode could be considered superior to other standard approaches that ask for participant responses about a longer time frame. Additional steps were taken to manage any potential recall bias, by asking the same questions across both episodes.

Investigation of situational variation within individuals has potential to inform clinical assessment and intervention for promoting adherence. Knowledge of the factors that vary over time or by situation rather than studying 'good adherers' versus 'bad adherers' could lead to the development of realistic, practical strategies to improve adherence or minimise non-adherence. This will be discussed in further detail below (see 'Clinical Implications').

Theoretical Implications

The results from the study demonstrate good reliability of the IMB constructs as measured situationally. The IMB model was not designed for use in within-participants comparison studies and has not been tested in this way. Some of the key relationships highlighted in the model, particularly the association between adherence behavioural skills and positive affect, were supported in this study. This suggests a robustness of some aspect of the IMB theoretical model.

Most health behaviour theories and intervention models highlight importance of motivation, but do not explain how motivation is enacted. Insufficient power for the analysis in the present study prevents reliable conclusions from being drawn regarding the exact influence of motivation on episodic adherence. However, the difference in effect sizes may indicate a differential influence of social and personal motivation between adherent and non-adherent events, with the latter not significantly implicated. Secondly, the IMB model's key emphasis on behavioural skills, or the closely related construct of self-efficacy, in carrying out a behaviour, was also demonstrated as key in the current study. There was a very large effect of behavioural skills between episodes of adherence. In relation to health-behaviour theory, this suggests the importance of constructs relating to self-efficacy as a crucial determinant of episodic adherence, rather than a focus on motivational constructs, which had little relationship with adherence in the current findings.

The IMB model, like many theories of health behaviour, neglects the influence of contextual factors such as those under investigation here. The current findings may suggest a significant impact of situational variables on episodic adherence that cannot be adequately explained by the IMB model. Other frameworks, including Social Action Theory (Ewart, 1991), describe mechanisms by which social and environmental structures influence health behaviours. It may be that such frameworks are beneficial in describing the event-level differences in adherence behaviour.

Clinical Implications

It may be of clinical importance to focus on the situational factors related to specific episodes of adherence and non-adherence to enable idiosyncratic assessment of barriers and promotion of facilitators of adherence. This novel within-subjects approach may be especially useful in developing and improving adherence assessments and interventions. Rather than distinguishing between generally good and poor adherers, this design highlights the resources within an individual. Understanding the situational relationship between adherent and non-adherent episodes could be useful for implementing more successful interventions. The identification of an individual's resources to help overcome barriers is central to a number of psychological interventions, including those used to promote ART adherence, such as Motivational Interviewing (Mbuagbaw et al., 2015; Mbuagbaw, Ye, & Thabane, 2012)and cognitive-behavioural techniques (Wagner, et al, 2006).

This study highlights behavioural skills as potentially critical for episodic ART adherence, suggesting that key areas for intervention could be: improving confidence to overcome barriers, promoting abilities in acquiring personal and social support, incorporating ART into daily life, self-cueing and self-reinforcement to adhere to ART (Fisher et al., 2006). The difference in the behavioural skills construct between variables could suggest that confidence to overcome barriers to adherence is both important and alterable.

Arrivillaga and colleagues reviewed adherence promotion interventions for adolescents that focused on managing the factors associated with adherence (Arrivillaga, Martucci, Hoyos, & Arango, 2013). Of ten published studies, the interventions involved: skills and knowledge education, social support and motivational interviewing. The most recent motivational interviewing (MI) programmes to promote adherence in young people are computer based and delivered online. A pilot study of two sessions of MI focused on a young person's perception of the importance of ART and their confidence in adhering (Outlaw et al., 2013). Ten young people, age 18-24, were enrolled, targeted adherence-related goal setting and planning, drawing on past successes and personal strengths. There was no adherence outcome measure in this pilot, however 100% of the sample improved in their perceptions of how important adherence was for them; 80% of the sample improved on subjective confidence. This intervention would be supported by the findings and the approach of the current study, which highlights the importance of perceived confidence in abilities to adhere and on facilitators of previous adherent episodes.

Blame is targeted in compassion-focused or cognitive-behavioural interventions, some of which have been applied to ART adherence behaviours but have not been adequately tested for effectiveness. However, if blame is a significant contextual barrier associated with non-adherence, this would support the development of additional interventions based on these approaches.

The findings presented here underline a particular difference of situational mood between episodes of adherence and non-adherence. Assessments of barriers to and facilitators of adherence could focus on contextual variations in mood and confidence. A greater understanding of these fluctuations would help health care professionals to identify which changes in mood are related to non-adherence with a particular individual. Normalising fluctuations in affect may help to engage with an intervention focused on idiosyncratic non-adherence patterns and planning for situations with a greater risk of non-adherence. Advanced planning may take the form of problem-solving strategies (Gross et al., 2013) or implementation intentions (Brandstätter et al., 2001; Schweiger Gallo & Gollwitzer, 2007; Sheeran et al., 2005).

The findings of this study also have implications for indirect adherence interventions, or strategies that can be used amongst healthcare professionals. Although guidelines consistently recommend assessment of readiness to adhere to a (potentially lifelong) ART regimen and barriers that may impede this, there is no specific guidance on how to go about this. The current study suggests particular areas for targeted assessment, including potential *facilitators*. The situational differences found in this study highlights the importance of detailed questioning about context. It might be important to ask about changes in both practical and emotional circumstances that have previously accompanied *both* adherent and non-adherent episodes. The findings from the present study highlight day of the week, location and disruption to routine as particular areas of focus to assess barriers to non-adherence and facilitators of adherence.

Further Research

The prime implication for developing this research would be to recruit a larger sample size. Primarily, this would support multivariate analysis and enable the situational variables to be included in a conditional logistic regression model, to explore the significant psychological relationships when controlling for behavioural situation. This would also facilitate additional analysis of factors such as age, gender, and type of medication as related to the significant variables between episodes. A larger number of participants would also increase the cell sizes for the categorical variables, which would remove the data-grouping requirement (e.g. grouping into 'alone' and 'not alone') and enable the analysis of each variable individually (e.g. 'alone', 'with family', 'with friend', 'with partner', etc).

It may be of interest to expand the data collection to include more than one adherent and non-adherent episode. The responses given in reference to particular episodes in the current study may not be representative of general adherent or non-adherent events for the sample. A greater number of specific episodes would allow for comparisons across multiple contexts. An episodic design allows one to take a longitudinal approach. This would also allow for comparisons within as well as between individuals over a longer period.

In focusing on situational variation, this study was not intended to investigate the neurocognitive correlates of adherence; participants' cognitive abilities would almost certainly remained static over the course of this investigation. However,

given what is known about the possible cognitive deficits in PHIV+ young people and the implication of various cognitive processes, particularly executive function (Nichols et al., 2012), working memory (Laughton et al., 2013) and prospective memory (Zogg, Woods, Sauceda, Wiebe, & Simoni, 2011), in medication adherence, it would be of interest to investigate whether there is any impact of cognition on the situational factors found to be associated with episodic adherence when controlling for cognitive ability.

The length of the prospective questionnaire may have been off-putting for some participants. Completion time was approximately 10-15 minutes per episode, not including getting to the website. Although this was an acceptable time in clinics and for a retrospective report, it may have been more difficult to schedule outside of the initial study session. Previous studies using EMA methods have found asking questions about affect and self-efficacy using a single question to be acceptable in their reliability and validity when data is collected repeatedly over several time points. An alternative approach to the prospective questionnaire could be to prompt participants to complete fewer questions and over shorter intervals and on more occasions.

The response rate to the prospective component of the study may also be improved using smartphone app technology, for example. Runyan and colleagues (2013) developed a specific ecological momentary assessment app, which conveniently prompted participants to rate a particular aspect of their behaviour at random or at

time intervals determined by the researchers. Although this methodology would require participants to possess a smartphone, there would be considerable benefits for data collection, particularly regarding the flexibility for both investigators and participants. In addition, this technology has the potential for Ecological Momentary Intervention (EMI) approaches to be trialled. That is, even in individuals not expressly seeking change, or, in the case of PHIV+ ART adherence, not expressly seeking to improve their medication taking, a set of timely, changeable cues could be sent via the app, relating to the particular individual context. This approach was successful in first year undergraduates who became more self-aware regarding productive use of time through the EMA monitoring (Runyan et al., 2013). The students were sent notifications to complete a short survey between five and seven times per day at random intervals (within waking hours). This repeated measurements allowed the authors to compare how much variation there was within-participants in how they spent their time over the week and test for possible differences day-to-day. Users reported an increase in self-awareness in how their time was spent over the study period as they became accustomed to using the app. Qualitative feedback from this pilot suggested that an increase in self-awareness prompted participants to alter their behaviour. In the case of PHIV+ youth, using a similar app to monitor the contextual factors under investigation in the present study may lead to greater awareness of patterns of behaviour in relation to episodic adherence and non-adherence and may prompt some users to change their routines accordingly. A more structured EMI approach has been trialled in patients with Borderline Personality Disorder with comorbid substance misuse problems. In this

case, the app has been used as a Dialectical Behaviour Therapy coach (Rizvi, Dimeff, Skutch, Carroll, & Linehan, 2011). There are possible applications of this method to adolescents' adherence interventions, whereby EMI apps could be used for in vivo skills coaching to promote self-efficacy and positive affect at the time of ART dose.

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Appendices

Appendix 1

NHS
Health Research Authority

NRES Committee South Central - Berkshire B
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421331
Fax:01173420445

29 May 2014

Ms Amy L Hawkins
Clinical Psychology Department, Royal Holloway University of London
Egham Hill
Egham
TW20 0EX

Dear Ms Hawkins

Study title:	**A within-subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV**
REC reference:	**14/SC/1019**
IRAS project ID:	**154311**

The Proportionate Review Sub-Committee of the NRES Committee South Central - Berkshire B reviewed the above application on 29 May 2014.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

1. Changes to the Participants Information sheet:
    a. Add the following statement "The study has been given a favourable opinion by the Berkshire B Research Ethics Committee".
    b. Submit separate PIS's for 12- 15 year olds, 16-18 year olds and 18 years and over.
    c. Simplify the language in the PIS for the 12-15 age group (e.g. Clinical Psychology doctorate course).

2. Confirm why some of the answers in the ITEM questionnaire are in red and whether this might affect the responses.

3. Confirm that parental / carer consent will be sought for children 12- 15.

4. Update either the protocol or PIS to ensure the time that the SMS text will be stopped is consistent (the protocol states that SMS text will be stopped after 1 month but the PIS states SMS will stop after 4 weeks and this needs to be consistent).

When submitting your response, please send the revised documentation underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to the Chair .

Please contact Stephanie Macpherson, 0117 342 1331 if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response.

Documents reviewed

The documents reviewed were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	1	02 September 2013
IRAS Checklist XML [Checklist_23052014]		23 May 2014
Non-validated questionnaire	0.2	19 May 2014
Participant consent form	1.2	19 May 2014
Participant information sheet (PIS) [12-15 with Pics]	1.2	19 May 2014
Participant information sheet (PIS) [16-21]	1.2	19 May 2014
REC Application Form [REC_Form_23052014]		23 May 2014
Research protocol or project proposal [RHUL major project proposal]	1.0	28 March 2014
Summary CV for Chief Investigator (CI) [Amy Hawkins]		05 February 2014
Summary CV for supervisor (student research) [Dr Michael Evangeli]		17 February 2014

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

14/SC/1019	**Please quote this number on all correspondence**

Yours sincerely

Pp Dr John Sheridan
Chair

Email: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: Dr Michael Evangeli, Royal Holloway University of London
michael.evangeli@rhul.ac.uk

Kirsty Hedditch, King's College Hospital NHS Foundation Trust
Kch-tr.research@nhs.net

NRES Committee South Central - Berkshire B

Attendance at PRS Sub-Committee of the REC meeting on 29 May 2014

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Michael Arnott	Consultant Research Services	Yes	
Mr Yash Patel	Research Support Associate	Yes	
Dr John Sheridan (chair)	Consultant Toxicologist and Chemist	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Stephanie Macpherson	REC Manager

Appendix 2

NRES Committee South Central - Berkshire B
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1331

27 June 2014

Ms Amy L Hawkins
Clinical Psychology Department
Royal Holloway University of London
Egham Hill
Egham
TW20 0EX

Dear Ms Hawkins

Study title:	**A within-subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV**
REC reference:	**14/SC/1019**
IRAS project ID:	**154311**

Thank you for your letter of 27 June 2014, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Miss Stephanie MacPherson, nrescommittee.southcentral-berkshireb@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	1	02 September 2013
IRAS Checklist XML [Checklist_23052014]		23 May 2014
Non-validated questionnaire [Questionnaire (Tracked Copy)]	0.2	10 June 2014
Participant consent form [Young Person (13-15 Year Olds) Assent Form (Tracked Copy)]	1.2	10 June 2014
Participant consent form [Parental Consent Form (Tracked Copy)]	1.2	10 June 2014
Participant information sheet (PIS) [16-18 Year Olds (Tracked Copy)]	1.1	03 June 2014
Participant information sheet (PIS) [18-21 Year Olds (Tracked Copy)]	1.1	03 June 2014
Participant information sheet (PIS) [13-15 Year Olds (Tracked Copy)]	1.4	14 June 2014
REC Application Form [REC_Form_23052014]		23 May 2014
Research protocol or project proposal [(Tracked Copy)]	1.2	10 June 2014
Response to Request for Further Information		14 June 2014
Summary CV for Chief Investigator (CI) [Amy Hawkins]		05 February 2014
Summary CV for supervisor (student research) [Dr Michael Evangeli]		17 February 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SC/1019	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp Dr John Sheridan
Chair

Email: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Kirsty Hedditch, kch-tr.research@nhs.net*

Appendix 3

NHS
Health Research Authority

NRES Committee South Central - Berkshire B

Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Tel: 0117 342 1387

10 February 2015

Ms Amy L Hawkins
Clinical Psychology Department, Royal Holloway University of London
Egham Hill
Egham
TW20 0EX

Dear Ms Hawkins

Study title:	**A within-subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV**
REC reference:	**14/SC/1019**
Amendment number:	**1**
Amendment date:	**09 February 2015**
IRAS project ID:	**154311**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	1	09 February 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SC/1019:	**Please quote this number on all correspondence**

Yours sincerely

PP
Dr John B Sheridan
Chair

E-mail: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Kirsty Hedditch, King's College Hospital NHS Foundation Trust*

NRES Committee South Central - Berkshire B

Attendance at Sub-Committee of the REC meeting on 13 February 2015

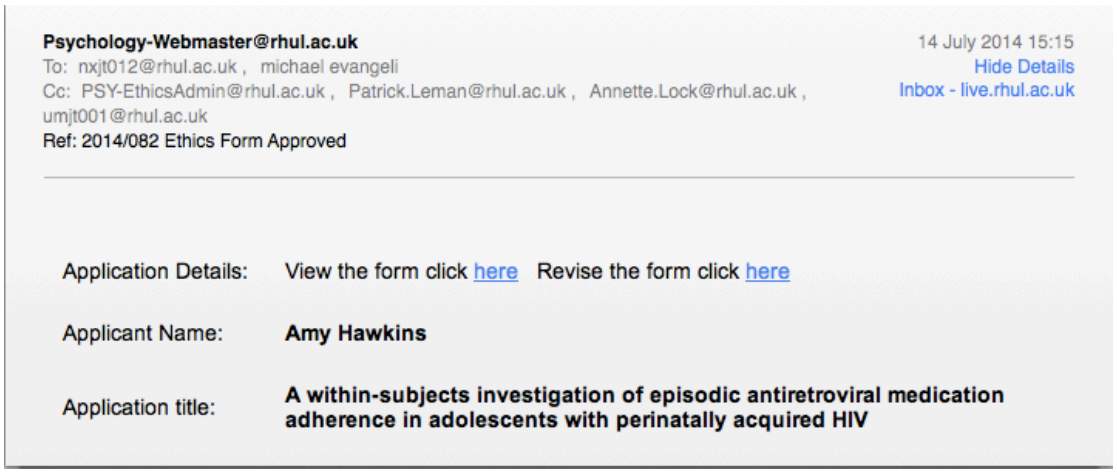
Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Mike Arnott	Research Consultant	Yes	
Dr John B Sheridan (Chair)	Consultant Toxicologist and Chemist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Lauren Allen	REC Manager

Appendix 4



Psychology-Webmaster@rhul.ac.uk
To: nxjt012@rhul.ac.uk , michael evangeli
Cc: PSY-EthicsAdmin@rhul.ac.uk , Patrick.Leman@rhul.ac.uk , Annette.Lock@rhul.ac.uk , umjt001@rhul.ac.uk
Ref: 2014/082 Ethics Form Approved

14 July 2014 15:15
Hide Details
Inbox - live.rhul.ac.uk

Application Details:	View the form click here Revise the form click here
Applicant Name:	**Amy Hawkins**
Application title:	**A within-subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally acquired HIV**

Appendix 5

The Pennine Acute Hospitals NHS Trust

Research and Development Department
Trust Headquarters, 1st Floor, Room 137
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
M8 5RB
T: 0161 604 5233

Dr. Steve Woby – Director of R&D
Steve.Woby@pat.nhs.uk

Katie Doyle – Research Operations Manager
Katie.Doyle@pat.nhs.uk

Charlotte Lever – R&D Quality & Performance Manager
Charlotte.Lever@pat.nhs.uk

Zoe Drinkwater – Research & Development Coordinator
Zoe.Drinkwater@pat.nhs.uk

Claire Carty – Research & Development Administrator
Claire.carty@pat.nhs.uk

Dr Paddy McMaster - Consultant in Paediatric Infectious Diseases
Limbert House
North Manchester General Hospital
Delaunays Road, Crumpsall
Manchester M8 5RB

09 April 2015

Dear Dr McMaster,

Re: Research & Development (R&D) approval (externally sponsored Non CTIMP)

R&D Reference Number:	**15PAED01**
CSP study ID:	**N/A (NON NIHR)**
Project Title:	**A within subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV**
Short Title:	**Episodic medication adherence in PHIV+ adolescents (PHIV)**
Ethics Reference:	**14/SC/1019**
Sponsor:	**Royal Holloway University of London**
Site:	**NMGH**
Recruitment start date:	**09.04.2015**
Recruitment end date:	**31.07.2015**
Number of participants to be recruited/ obtained at site:	**12 for the duration of the study**

Thank you for providing the Research & Development (R&D) department with your research project information. The above study was considered by The Pennine Acute Hospitals NHS Trust in line with the Research Governance Framework where based on the information provided the impact of the

study on the Trust's resources was reviewed. I am pleased to inform you that the study has received Trust R&D approval.

Following verification of relevant Regulatory approval from The National Research Ethics Service, the following documents as listed on the ethics approval letter have been approved by R&D:

IRAS amendment form listing Pennine as a site
Signed SSI form for The Pennine Acute Hospitals NHS Trust
Ethics approval letters dated 10.02.3015, 27.06.2014
Protocol (Version 1.2) dated 10.06.14
Any other documents listed on Ethics letter dated 27.06.2014
Email from Katie Doyle to Dr McMaster dated 31.03.15 enclosing protocol V 1.2 and SSI form. Dr McMaster confirmed receipt and feasibility by signing the front page of the SSI.
Signed & dated CVs for those listed on the SSI form
GCP certificates for Dr McMaster and Katie Rowson

If there are any substantial amendments to the protocol, including the number of patients to be recruited from The Pennine Acute Hospitals NHS Trust, you must obtain a favourable opinion from:

- The National Research Ethics Service
- The Pennine Acute Hospitals NHS Trust (please note that all amendment documentation as approved by The Research Ethics Committee (REC) must be submitted to the R&D department)

On completion of the study you are required to submit a 'Declaration of End of Study' form to the main REC, which should also be copied and forwarded to the R&D Department at the above address.
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/

As part of research governance the R&D department is expected to monitor the progress of registered projects. Therefore, on-going projects may be subject to random inspection. Your research must be conducted in compliance with the NHS Research Governance Framework for Health & Social Care.
http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/Researchgovernance/DH_4002112

It is a condition of NHS R&D approval that patient recruitment data should be forwarded on a regular basis. Therefore, project reports must be submitted annually to the main REC and copied to the R&D office until the end of the study.
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

In addition to your obligations to the study organisers and the REC, the R&D Department must be informed of any governance issues related to the research.

Failure to comply with any of the above may result in withdrawal of approval for the project and the immediate cessation of the research.

Yours sincerely

Dr. Steve Woby
Director of Research & Development

cc: **Katie Rowson (Research Nurse) - katie.rowson@pat.nhs.uk**
Amy Hawkins (Trainee Clinical Psychologist) - amy.hawkins.2012@live.rhul.ac.uk

Appendix 6

Direct Line:
02087253784
Email:
akadchha@sgul.ac.uk

26/08/2014

Dr Katia Prime
Consultant in HIV and Sexual Health
St George's Hospital NHS Trust
Courtyard Clinic, Department of GUM
St George's Hospital, Blackshaw Road
London
SW17 8HN

Dear Dr Katia Prime,

PROJECT TITLE	A within subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV
REC Reference	14/SC/1019
JREO Reference	14.0168
CSP Reference (if applicable)	N/A
Sponsor	Royal Holloway University of London
Principal Investigator (PI):	Dr Katia Prime

Notification of St George's Healthcare NHS Trust host site permission

Permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed and approved were those specified in the ethics approval letter dated 27/06/2014. The protocol version approved is version v1.2 dated 10/06/2014

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, and NHS Trust policies. Permission is only granted for the activities for which a favourable opinion has been given by the REC. The permission may be invalidated in the event that the terms and conditions of any research contract or agreement change significantly and while the new contract/agreement is negotiated.

The research sponsor, the Chief Investigator, or the local Principal Investigator, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The JREO should be notified that such measures have been taken. The notification should also include the reasons why the measures were

taken and the plan for further action. The JREO should be notified within the same time frame of notifying the REC.

All amendments to this study (including changes to the local research team) need to be submitted in accordance with the guidance on IRAS. In addition any changes to the status of a study should be notified to the JREO.

Please note that the JREO is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements.

Any intellectual property that is identified should be discussed with the JREO prior to any disclosure of this information by publication or presentations to ensure that all rights are protected.

At study closure, the JREO together with the approving ethics committee should be notified that the study is closed. Study findings should be disseminated as identified in the original ethics application (including participants where appropriate). Study files should be appropriately archived.

Please contact the JREO if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely

Anika Kadchha
On behalf of SGUL/SGHT
Joint Research and Enterprise Office

Appendix 7

12/11/2014

King's College Hospital NHS
NHS Foundation Trust

Dr Emily Cheserem
King's College Hospital
Denmark Hill, London
SE5 9RS
UK

The Research Office
Kings College Hospital NHS Foundation Trust
First Floor 161 Denmark Hill,
London, SE5 8EF

Direct tel: 020 3299 1980
Direct fax: 020 3299 5515

www.kch.nhs.uk/research
kch-tr.research@nhs.net

Dear Dr Cheserem,

Study Title: A within subjects investigation of episodic antiretroviral medication adherence in adolescents with perinatally infected HIV
Ethics ref: 14/SC/1019
Sponsor: Royal Holloway University of London
Location: Denmark Hill
Study duration: 6 Months
Target Recruitment: 15 Participants
Protocol Version: version 1.2 dated 10/06/14

On behalf of **King's College Hospital NHS Foundation Trust,** I am pleased to inform you that your project is approved and you may proceed.

The study has been registered as **KCH14-173**. Please quote this reference in any communications with the Research Office regarding your project.
All approved documents are listed at the end of this letter. Please ensure that any amendments to the documents or changes to the study team are notified to the office.

Investigator Responsibilities:

You are expected to recruit to time and target. A condition of the approval is to notify the Research Office of the date of first recruitment at the above email address.
The approval is conditional on the project being conducted as described within the application. The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures - especially those relating to research and data management.
You must notify the office of all changes to the project, such as amendment to protocol and changes in study team. An end of study report and copies of the yearly REC report should be submitted to R&D.

V3 Sept 2014

You are responsible for ensuring that good research governance, conduct and practice, are maintained throughout the duration of the study.
The Trust maintains oversight of all active projects and you may be subject to review and audit at any point by internal or external bodies.
If the project is a clinical trial under the European Union (EU) Clinical Trials Directive the EU legislation must be complied with.

If appropriate it is recommended that you register with the Current Controlled Trials website; http://isrctn.org/

The Research office will support you throughout the duration of your project. Please contact us at the address above if and when you require further information or guidance.

We wish you every success with your project.

Yours sincerely,

Abdul Babalola
Research Governance Coordinator

cc. Chief Investigator: Amy Hawkins, Royal Holloway University of London, Amy.Hawkins.2012@live.rhul.ac.uk>

cc. Sponsor: Andy Macleod, Royal Holloway University of London, a.macleod@rhul.ac.uk

List of Approved Documents

Title	Version	Date
Participant information sheet - 13-15 Year Olds	1.4	14/06/14
Participant information sheet - 18-21 Year Olds	1.1	3/06/14
Participant information sheet - 16-18 Year Olds	1.1	3/06/14
Participant consent form - Young Person (13-15 Year Olds) Assent Form	1.2	10/6/14
Participant consent form - Parental Consent Form	1.2	10/06/14
Questionnaire	1.6	24/10/14

V3 Sept 2014

The LifeWindows Information-- Motivation -- Behavioral Skills ART Adherence Questionnaire (LW-IMB-AAQ) ITEMS

Note: Each LW-IMB-AAQ item represents a barrier primarily falling within the I (Information), M (Motivation), or B (Behavioral Skills) constructs. When used with the LifeWindows ART adherence intervention software program, a 'critical zone' is superimposed for a range of response options for each item (reflected here as shaded and in red text). Responses within the critical zone are interpreted as signaling the presence of a deficit or potential deficit that then triggers the offering of intervention activities specifically developed to address the barrier reflected in the content of the item.

I1 I know how each of my current HIV medications is supposed to be taken (for example whether or not my current medications can be taken with food, herbal supplements, or other prescription medications).

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I2 I know what to do if I miss a dose of any of my HIV medications (for example, whether or not to take the pill(s) later).

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I3 Skipping a few of my HIV medications from time to time would not really hurt my health.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I4 I know what the possible side effects of each of my HIV medications are.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I5 As long as I am feeling healthy, missing my HIV medications from time to time is OK.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I6 I understand how each of my HIV medications works in my body to fight HIV.

☐	☐	☐	☐	☐
I strongly disagree	I somewhat disagree	I neither agree nor disagree	I somewhat agree	I strongly agree

I7 If I don't take my HIV medications as prescribed, these kinds of medications may not work for me in the future.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

I8 I believe that if I take my HIV medications as prescribed, I will live longer.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

I9 I know how my HIV medications interact with alcohol and street drugs.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M1 I am worried that other people might realize that I am HIV+ if they see me taking my HIV medications.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M2 I get frustrated taking my HIV medications because I have to plan my life around them.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M3 I don't like taking my HIV medications because they remind me that I am HIV+.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M4 I feel that my healthcare provider takes my needs into account when making recommendations about which HIV medications to take.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M5 Most people who are important to me who know I'm HIV positive support me in taking my HIV medications.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly Agree ☐ No one that I care about knows I am positive

M6 My healthcare provider doesn't give me enough support when it comes to taking my

medications as prescribed.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M7 It frustrates me to think that I will have to take these HIV medications every day for the rest of my life.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M8 I am worried that the HIV medications I have been prescribed will hurt my health.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M9 It upsets me that the HIV medications I have been prescribed can affect the way I look.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

M10 It upsets me that the HIV medications I have been prescribed can cause side effects.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree

B1 There are times when it is hard for me to take my HIV medications when I drink alcohol or use street drugs.

☐ I strongly disagree ☐ I somewhat disagree ☐ I neither agree nor disagree ☐ I somewhat agree ☐ I strongly agree ☐ I don't drink alcohol or use street drugs

B2 How hard or easy is it for you to stay informed about HIV treatment?

☐ Very hard ☐ Hard ☐ Sometimes hard, sometimes easy ☐ Easy ☐ Very easy

B3 How hard or easy is it for you to get the support you need from others for taking your HIV medications (for example, from friends, family, doctor, or pharmacist)?

☐ Very hard ☐ Hard ☐ Sometimes hard, sometimes easy ☐ Easy ☐ Very easy

B4 How hard or easy is it for you to get your HIV medication refills on time?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B5 How hard or easy is it for you to take your HIV medications when you are wrapped up in what you are doing?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B6 How hard or easy is it for you to manage the side effects of your HIV medications?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B7 How hard or easy is it for you to remember to take your HIV medications?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B8 How hard or easy is it for you to take your HIV medications because the pills are hard to swallow, taste bad, or make you sick to your stomach?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B9 How hard or easy is it for you to make your HIV medications part of your daily life?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B10 How hard or easy is it for you to take your HIV medications when your usual routine changes (for example, when you travel or when you go out with your friends)?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B11 How hard or easy is it for you to take your HIV medications when you do not feel good emotionally (for example, when you are depressed, sad, angry, or stressed out)?

Very hard	Hard	Sometimes hard, sometimes easy	Easy	Very easy
☐	☐	☐	☐	☐

B12 How hard or easy is it for you to take your HIV medications when you feel good physically and don't have any symptoms of your HIV disease?

☐ Very hard ☐ Hard ☐ Sometimes hard, sometimes easy ☐ Easy ☐ Very easy

B13 How hard or easy is it for you to take your HIV medications when you do NOT feel good physically?

☐ Very hard ☐ Hard ☐ Sometimes hard, sometimes easy ☐ Easy ☐ Very easy

B14 How hard or easy is it for you to talk to your health care provider about your HIV medications?

☐ Very hard ☐ Hard ☐ Sometimes hard, sometimes easy ☐ Easy ☐ Very easy

Information Sheet for Participants (age 13-15)
v1.4 14.06.14

Research title: Antiretroviral Medication Adherence in Young People with Perinatal HIV

We are asking you to take part in a research project to find out more about how young people take their HIV medicine
Before you decide if you want to join in, it is important you understand why the research is being done and what it will involve for you. Please read this leaflet carefully, think about it, and talk to your family, friends, or a member of your clinical team if you want to.

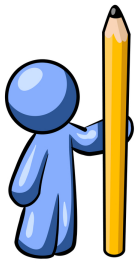
Why are we doing this research?
Some young people who were born with HIV have to take pills or medicines every day to keep healthy. We know that sometimes this might be easier to do than at other times. There might be some times when you don't take your medicine for some reason. We are interested in the reasons why you do and why you don't take your medicine. We hope that by asking young people about specific times when they do or don't take their medicine we will have a better idea of what the reasons for taking or not taking it might be.

This project is part of the training course for qualifying as a Clinical Psychologist at Royal Holloway University of London.

Who is invited to take part?
This research is open to young people aged 13-21 who were born with HIV. To take part, you must have **missed taking your medicines** at least once in the **last two months**. If you have taken all of your medicines (this means every time you should have) for the last two months, you won't be able to take part.

Do I have to take part?

No, it is up to you. If you are interested, we will ask you to fill out a form that says you agree to take part. If you change your mind, you are free to stop taking part without giving a reason at any point during the study. It will not affect the care you get at your HIV clinic if you decide to drop out of the study or don't want to take part.



What will I be asked to do?

There are 2 parts to the study:

Part 1

We will ask you to remember a time in the last two months when you ***did*** take your medicine and ask you to answer some questions about it. Then we will ask you about a time when you ***did not*** take your medicine and ask you to answer some questions about it. The questions will be about how you were feeling, what you were thinking and what was going on at the time. You can fill-in these questions on paper or online, whichever you prefer. You will receive a £10 voucher for taking part in this section of the project.

Part 2

If you agree, we will send you text messages every day for four weeks to remind you to complete the questionnaires again for a time when you ***do*** and a time if you ***don't*** take your medicine.

These questionnaires will be online. You won't get any more text messages after the four weeks is up or after you have answered the questions for both the time that you **did** and the time you **did not** take your medicine. If you decide to take part in this section of the project, you will be entered into a prize draw to receive an extra £50 of vouchers.

What are the possible benefits of taking part?

There might not be any direct benefit to you straightaway. But if we can understand what makes it easier or more difficult for young people to take their medicine, we might be able to help other people like you to manage their medicine better in the future.

Will anyone else know I'm doing this?

We will keep your information private and store it securely. This means only the research team will be able to access it. Your name won't be kept with any of your questionnaires; we will only be able to identify you through a unique code. We will not tell your healthcare team any of the answers to the questionnaires that you fill in.

What happens if I don't want to carry on with the study?

You can leave the study at any time. If you decide you don't want to take part any more, we will not use any of the answers you have given us on the questionnaires, delete any information that could identify you and not contact you again.

What if there is a problem?

If you are worried about any part of the project, you should ask to speak to the main researcher, Amy Hawkins, who will do her best to help you. Her contact details are below. You can also contact Kate Sturgeon, AALPHI Research Nurse, on 07500975776. If you get upset by any of the questions you can also get help from Amy or Kate.

What happens after the research project stops?
We will let you know what we find out from the project after it is finished. We will leave a leaflet in your clinic for you to read and there will be a summary in the AALPHI newsletter.

We hope to publish the results in an academic journal, so other researchers can know about our findings. We might also want to present the results at conferences so that we can help clinicians to help other young people with taking their medication. You won't be identified in any reports or articles.

Who has reviewed this study?
Before any research goes ahead, it has to be checked by a Research Ethics Committee. They make sure that the research is safe and fair. The study has been given a favourable opinion by Berkshire B Research Ethics Committee, checked by NHS Research & Development and Royal Holloway Departmental Ethics Committee.

Thank you for reading this. Please ask any questions if you need to.

Contact details
The main person to contact for this project is Amy Hawkins, Trainee Clinical Psychologist, at the Department of Clinical Psychology, Royal Holloway University of London (RHUL). You can get in touch in the following ways if you have any questions about the research at any time.

Email: amy.hawkins.2012@live.rhul.ac.uk
Phone: 01784 414012 (this is an answering machine – please say your message is for Amy Hawkins, leave your contact details and a brief message and I will call you back)
Address: Dept. of Clinical Psychology, RHUL, Egham Hill, Egham, Surrey, TW20 0EX.

There will be a form for you to fill in if you want to take part.

Information Sheet for Participants (age 16-18)

v1.1 03.06.14

Research title: Antiretroviral Medication Adherence in Young People with Perinatally-Infected HIV

We are asking you to take part in a research project to find out more about how young people take their medication.
Before you decide if you want to participate, it is important you understand why the research is being done and what it will involve. Please consider this leaflet carefully and talk to your family, friends, doctor or nurse if you want to.

Why are we doing this research?
Young people who were born with HIV have to take medication every day to keep healthy. We know that sometimes this might be easier to do than other times. There might be some times when you don't take your medication for some reason. We are interested in what influences whether you do or do not take your medication by asking you about actual times recently when you did or did not take it. We hope that by asking young people about specific times when they do or don't take their medication we will have a better idea of what the reasons for taking or not taking it might be.

This project is being carried out as part of a Clinical Psychology doctorate course at Royal Holloway University of London.

Who is invited to take part?
This research is open to young people age 12-21 who were born with HIV. To take part, there must have been a time in the **last two months** when you **did not take** your medication. If you have taken your medication every day for the last two months, you won't be able to take part.

Do I have to take part?

No, it is up to you. If you are interested, we will ask you to complete a form that says you agree to take part. If you change your mind, you are free to stop taking part without giving a reason at any point during the research. Your healthcare will not be affected in any way if you decide to withdraw from the study.

What will I be asked to do?

There are 2 parts to the study:

Part 1

We will ask you to remember a time in the last two months when you ***did*** take your medication and a time when you ***did not*** take your medication . We will ask you to answer questions about each of these times. The questions will be about how you were feeling, what you were thinking and what was going on at the time, for example. You can fill-in these questions on paper or online, whichever you prefer. You will receive a £10 voucher for taking part in this section of the project.

Part 2

If you agree, we will also ask you to answer the same questions for one further time that you **did** and one further time that you **did not** take your medication in the four weeks after you sign up to the study. We will send you text messages to remind you to do this every day until you have answered the questions for one time that you **did** and one time that you **did not** take your medication. These questionnaires will be online. You won't get any more text messages after the four weeks is up or after you have answered the questions for both the time that you **did** and the time you **did not** take your medication (whichever is the soonest). If you decide to take part in this section of the project, you will be entered into a prize draw to receive an extra £50 of vouchers.

What are the possible benefits of taking part?

There might not be any direct benefit to you straightaway. But if we can understand what makes it easier or more difficult for young people to take their medication, we might be able to help other people like you to manage in the future.

Will anyone else know I'm doing this?

We will keep your information in confidence and store it securely on an encrypted memory stick. This means only the research team will be able to access it. Your name won't be kept with any of your questionnaires; we will only be able to identify you through a unique user code. We might tell your healthcare team that you are taking part, but we will not tell them any of the answers to the questionnaires that you fill in.

What happens if I don't want to carry on with the study?

If you decide you don't want to take part any more, we will not use any of the answers you give us on the questionnaires and delete any information that could identify you.

What if there is a problem?

If you have a concern about any part of the project, or in the unlikely event that you become upset or distressed by the questions, you should ask to speak to the main researcher, Amy Hawkins, who will do her best to help you. Her contact details are below. You can also contact Kate Sturgeon, AALPHI Research Nurse, on 020 7670 4862.

What happens after the research project stops?
We will let you know what we find out from the project after it is finished. We will send you a leaflet for you to read and there will be a summary in the AALPHI newsletter.

We hope to publish the results in an academic journal, so other researchers can know about our findings. We might also want to present the results at conferences so that we can help clinicians to help other young people with taking their medication. You won't be identified in any reports or articles.

Who has reviewed this study?
Before any research goes ahead, it has to be checked by a Research Ethics Committee. They make sure that the research is safe and fair. This project has been given a favourable opinion by Berkshire B Ethics Committee, and checked by NHS Research & Development and Royal Holloway Departmental Ethics Committee.

Thank you for reading this. Please ask any questions if you need to.

Contact details
The main person to contact for this project is Amy Hawkins, Trainee Clinical Psychologist, at the Department of Clinical Psychology, Royal Holloway University of London (RHUL). You can get in touch in the following ways if you have any questions about the research at any time.

Email: amy.hawkins.2012@live.rhul.ac.uk
Phone: 01784 414012 (this is an answering machine – please say your message is for Amy Hawkins, leave your contact details and a brief message and I will call you back)
Address: Dept. of Clinical Psychology, RHUL, Egham Hill, Egham, Surrey, TW20 0EX.

There will be a form for you to fill in if you want to take part.

Information Sheet for Participants (age 18-21)

v1.1 03.06.14

Research title: Antiretroviral Medication Adherence in Young People with Perinatally-Infected HIV

We invite you to take part in a research project investigating how young people take their medication.
Before deciding if you want to participate, it is important you understand why the research is being done and what it will involve. Please consider this leaflet carefully and talk to your family, friends, doctor or nurse if you want to.

Why are we doing this research?
Young people who were born with HIV often have to take daily medication to stay healthy. We know that sometimes this might be easier to do than other times. There might be some times when you don't take your medication for some reason. We are interested in what influences whether you do or do not take your medication by asking you about actual times recently when you did or did not take it. We hope that by asking young people about specific times when they do or don't take their medication we will have a better idea of what the reasons for taking or not taking it might be.

This project is being carried out as part of a Clinical Psychology doctorate course at Royal Holloway University of London.

Who is invited to take part?
This research is open to young people age 12-21 who were born with HIV. To take part, there must have been a time in the **last two months** when you **did not take** your medication. If you have taken your medication every day for the last two months, you won't be able to take part.

Do I have to take part?

No, it is up to you. If you are interested, we will ask you to complete a form that says you agree to take part. If you change your mind, you are free to stop taking part without giving a reason at any point during the research. Your healthcare will not be affected in any way if you decide to withdraw from the study.

What will I be asked to do?

There are 2 parts to the study:

Part 1

We will ask you to remember a time in the last two months when you ***did*** take your medication and a time when you ***did not*** take your medication. We will ask you to answer questions about each of these times. The questions will be about how you were feeling, what you were thinking and what was going on at the time, for example. You can fill-in these questions on paper or online, whichever you prefer. You will receive a £10 voucher for taking part in this section of the project.

Part 2

If you agree, we will also ask you to answer the same questions for one further time that you **did** and one further time that you **did not** take your medication in the four weeks after you sign up to the study. We will send you text messages to remind you to do this every day until you have answered the questions for one time that you **did** and one time that you **did not** take your medication. These questionnaires will be online. You won't get any more text messages after the four weeks is up or after you have answered the questions for both the time that you **did** and the time you **did not** take your medication (whichever is the soonest). If you decide to take part in this section of the project, you will be entered into a prize draw to receive an extra £50 of vouchers.

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There might not be any direct benefit to you straightaway. But if we can understand what makes it easier or more difficult for young people to take their medication, we might be able to help other people like you to manage in the future.

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What happens if I don't want to carry on with the study?

If you decide you don't want to take part any more, we will not use any of the answers you give us on the questionnaires and delete any information that could identify you.

What if there is a problem?

If you have a concern about any part of the project, or in the unlikely event that you become upset or distressed by the questions, you should ask to speak to the main

researcher, Amy Hawkins, who will do her best to help you. Her contact details are below. You can also contact Kate Sturgeon, AALPHI Research Nurse, on 020 7670 4862.

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We hope to publish the results in an academic journal, so other researchers can know about our findings. We might also want to present the results at conferences so that we can help clinicians to help other young people with taking their medication. You won't be identified in any reports or articles.

Who has reviewed this study?
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Thank you for reading this. Please ask any questions if you need to.

Contact details
The main person to contact for this project is Amy Hawkins, Trainee Clinical Psychologist, at the Department of Clinical Psychology, Royal Holloway University of London (RHUL). You can get in touch in the following ways if you have any questions about the research at any time.

Email: amy.hawkins.2012@live.rhul.ac.uk
Phone: 01784 414012 (this is an answering machine – please say your message is for Amy Hawkins, leave your contact details and a brief message and I will call you back)
Address: Dept. of Clinical Psychology, RHUL, Egham Hill, Egham, Surrey, TW20 0EX.

There will be a form for you to fill in if you want to take part.

Appendix 12

ROYAL HOLLOWAY UNIVERSITY OF LONDON

Consent Form

Version 1.1 10.03.14

Title of project: Medication adherence in young people with perinatally-infected HIV

Name of researcher: Amy Hawkins (amy.hawkins.2012@live.rhul.ac.uk)

Please tick the box if you agree

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information and ask questions. Any questions have been answered to my satisfaction. ☐

2. I understand that my participation is voluntary and I am free to withdraw at any time (without giving a reason, without my healthcare being affected). ☐

3. I understand that relevant sections of my medical notes and data collected by this study may be looked at researchers from Royal Holloway and AALPHI, from regulatory authorities or from the NHS Trust. I give permission for these individuals to have access to this information. ☐

4. I agree that my GP can be informed of my participation in this study. ☐

5. I agree to take part in the above study. ☐

Name of participant: _____

Date: _____

Signature: _____

Name of person taking consent: _____

Date: _____

Signature:_____

Appendix 13

RHUL ART Situational Adherence Questionnaire
v1.6 (24/10/14)

Think about the time when you **did take** your medication. Please answer these questions about what you thought and how you felt at that time.

What day of the week was it (when you did take your medication)?
…….

Was there someone there to remind you to take the medication at the time? (when you did take your medication) (please circle)

YES NO

Please tick which one applied to you at the time (when you did take your medication):

My day was the same as normal ☐
My day was different to normal because of something unexpected ☐
My day was different to normal because I had made plans ☐
Other ☐

Where were you? (when you did take your medication) **(please tick)**

Home ☐ A friend's house ☐ Partner's house ☐
A public place (e.g., work, college) ☐ A family member's house ☐

Who were you with? (when it was time to take your medication and you did take it) **(please tick)**

Alone ☐ With a friend ☐ With a partner ☐ With family ☐

With an acquaintance ☐ With a work colleague ☐

Were you using alcohol or taking street drugs (e.g. cannabis, ecstasy) around the time you were due to take your medicines? (please circle) YES NO

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I knew the correct way to take my medicines	Ç	Ç	Ç	Ç	Ç
I knew how taking the medication could make me feel	Ç	Ç	Ç	Ç	Ç
I understood how my medicines would work	Ç	Ç	Ç	Ç	Ç
I understood what medication to take	Ç	Ç	Ç	Ç	Ç
I thought other people would notice I was taking my medication, which concerned me	Ç	Ç	Ç	Ç	Ç
I thought I had to plan my life around my medicine, which frustrated me	Ç	Ç	Ç	Ç	Ç
The medicines reminded me I was HIV+, which bothered me	Ç	Ç	Ç	Ç	Ç
People around me that I care about were supportive about my medication	Ç	Ç	Ç	Ç	Ç
I thought that I would have to take these medicines every day for the	Ç	Ç	Ç	Ç	Ç

rest of my life, which I did not like					
I thought the medication was not working, which bothered me	Ç	Ç	Ç	Ç	Ç
I thought my medication was helping	Ç	Ç	Ç	Ç	Ç
I thought the medication was harming me	Ç	Ç	Ç	Ç	Ç
I thought my medication would cause side effects	Ç	Ç	Ç	Ç	Ç
I was bothered by the size, taste or amount of medication	Ç	Ç	Ç	Ç	Ç
I had easy access to my medicines	Ç	Ç	Ç	Ç	Ç
I was confident I could find the time to take my medication	Ç	Ç	Ç	Ç	Ç
I was confident I could manage any side effects	Ç	Ç	Ç	Ç	Ç
I was confident that I could remember to take my medicines	Ç	Ç	Ç	Ç	Ç
I was confident I could manage the size of the pills or the taste of the medicine	Ç	Ç	Ç	Ç	Ç
I felt confident that I could fit my medicines around what I was doing	Ç	Ç	Ç	Ç	Ç
I felt confident I could take my	Ç	Ç	Ç	Ç	Ç

medicines correctly					
I felt confident I could take my medicines even if other people were around	Ç	Ç	Ç	Ç	Ç
I felt confident I could ask for help to take my medication if I needed to	Ç	Ç	Ç	Ç	Ç
I felt confident I could take my medicines however I was feeling	Ç	Ç	Ç	Ç	Ç
I felt ill	Ç	Ç	Ç	Ç	Ç
Taking the medicines was my choice	Ç	Ç	Ç	Ç	Ç

How did you feel when it was time to take your medication?

	1 Very slightly	2 A little	3 Moderately	4 Quite a bit	5 Extremely
Proud	Ç	Ç	Ç	Ç	Ç
Happy	Ç	Ç	Ç	Ç	Ç
Scared	Ç	Ç	Ç	Ç	Ç
Lively	Ç	Ç	Ç	Ç	Ç
Afraid	Ç	Ç	Ç	Ç	Ç
Miserable	Ç	Ç	Ç	Ç	Ç
Joyful	Ç	Ç	Ç	Ç	Ç
Mad	Ç	Ç	Ç	Ç	Ç
Sad	Ç	Ç	Ç	Ç	Ç
Cheerful	Ç	Ç	Ç	Ç	Ç
Blamed	Ç	Ç	Ç	Ç	Ç
Weak	Ç	Ç	Ç	Ç	Ç
Helpless	Ç	Ç	Ç	Ç	Ç

Out of control	Ç	Ç	Ç	Ç	Ç
Calm	Ç	Ç	Ç	Ç	Ç
At ease	Ç	Ç	Ç	Ç	Ç
Content	Ç	Ç	Ç	Ç	Ç
Satisfied	Ç	Ç	Ç	Ç	Ç

ROYAL HOLLOWAY UNIVERSITY OF LONDON

RHUL ART Situational Adherence Questionnaire
v1.6(24/10/14)

Think about the time when you **did not take** your medication. Please answer these questions about what you thought and how you felt at that time.

What day of the week was it (when you did not take your medication)?
…….

Was there someone there to remind you to take the medication at the time? (when you did not take your medication) (please circle)

YES NO

Please tick which one applied to you at the time (when you did not take your medication):

My day was the same as normal ☐
My day was different to normal because of something unexpected ☐
My day was different to normal because I had made plans ☐
Other ☐

Where were you? (when it was time to take your medication and you did not take it) **(please tick)**

Home ☐ A friend's house ☐ Partner's house ☐

A public place (e.g., work, college) ☐ A family member's house ☐

Who were you with? (when you did not take your medication)

Alone ☐ With a friend ☐ With a partner ☐ With family ☐

With an acquaintance ☐ With a work colleague ☐

Were you using alcohol or taking street drugs (e.g. cannabis, ecstasy) around the time you were due to take your medicines? (please circle) YES NO

	1 Strongly disagree	2 Disagree	3 Neither agree or disagree	4 Agree	5 Strongly agree
I knew the correct way to take my medicines	Ç	Ç	Ç	Ç	Ç
I knew how taking the medication could make me feel	Ç	Ç	Ç	Ç	Ç
I understood how my medicines would work	Ç	Ç	Ç	Ç	Ç
I understood what medication to take	Ç	Ç	Ç	Ç	Ç
I thought other people would notice I was taking my medication, which concerned me	Ç	Ç	Ç	Ç	Ç
I thought I had to plan my life around my medicine, which frustrated me	Ç	Ç	Ç	Ç	Ç
The medicines reminded me I was HIV+, which bothered me	Ç	Ç	Ç	Ç	Ç
People around me that I care about were supportive					

about my medication	Ç	Ç	Ç	Ç	Ç
I thought that I would have to take these medicines every day for the rest of my life, which I did not like	Ç	Ç	Ç	Ç	Ç
I thought the medication was not working, which bothered me	Ç	Ç	Ç	Ç	Ç
I thought my medication was helping	Ç	Ç	Ç	Ç	Ç
I thought the medication was harming me	Ç	Ç	Ç	Ç	Ç
I thought my medication would cause side effects	Ç	Ç	Ç	Ç	Ç
I was bothered by the size, taste or amount of medication	Ç	Ç	Ç	Ç	Ç
I had easy access to my medicines	Ç	Ç	Ç	Ç	Ç
I was confident I could find the time to take my medication	Ç	Ç	Ç	Ç	Ç
I was confident I could manage any side effects	Ç	Ç	Ç	Ç	Ç
I was confident that I could remember to take my medicines	Ç	Ç	Ç	Ç	Ç
I was confident I could manage the size of the pills or the taste of the	Ç	Ç	Ç	Ç	Ç

medicine					
I felt confident that I could fit my medicines around what I was doing	Ç	Ç	Ç	Ç	Ç
I felt confident I could take my medicines correctly	Ç	Ç	Ç	Ç	Ç
I felt confident I could take my medicines even if other people were around	Ç	Ç	Ç	Ç	Ç
I felt confident I could ask for help to take my medication if I needed to	Ç	Ç	Ç	Ç	Ç
I felt confident I could take my medicines however I was feeling	Ç	Ç	Ç	Ç	Ç
I felt ill	Ç	Ç	Ç	Ç	Ç
I completely forgot	Ç	Ç	Ç	Ç	Ç

How did you feel when it was time to take your medication?

	1 Very slightly	2 A little	3 Moderately	4 Quite a bit	5 Extremely
Proud	Ç	Ç	Ç	Ç	Ç
Happy	Ç	Ç	Ç	Ç	Ç
Scared	Ç	Ç	Ç	Ç	Ç
Lively	Ç	Ç	Ç	Ç	Ç
Afraid	Ç	Ç	Ç	Ç	Ç
Miserable	Ç	Ç	Ç	Ç	Ç
Joyful	Ç	Ç	Ç	Ç	Ç
Mad	Ç	Ç	Ç	Ç	Ç
Sad	Ç	Ç	Ç	Ç	Ç

Cheerful	Ç	Ç	Ç	Ç	Ç
Blamed	Ç	Ç	Ç	Ç	Ç
Weak	Ç	Ç	Ç	Ç	Ç
Helpless	Ç	Ç	Ç	Ç	Ç
Out of control	Ç	Ç	Ç	Ç	Ç
Calm	Ç	Ç	Ç	Ç	Ç
At ease	Ç	Ç	Ç	Ç	Ç
Content	Ç	Ç	Ç	Ç	Ç
Satisfied	Ç	Ç	Ç	Ç	Ç

Do you have a medication regime? (please circle)

YES NO

Was there anything else important about the day you missed your medication? E.g. you were told not to take it by your doctor that day

……
……
……
……
……